Enantioselective desymmetrization reactions in asymmetric catalysis

Q5

Carmen Nájera[a,*], cnajera@ua.es, Francisco Foubelo[a,b], foubelo@ua.es, José M. Sansano[a,b], jmsansano@ua.es, Miguel Yus[a], yus@ua.es

[a]Centro de Innovación en Química Avanzada (ORFEO–CINQA), Universidad de Alicante, Apdo. 99, 03080, Alicante, Spain

[b]Departamento de Química Orgánica and Instituto de Síntesis Orgánica, Universidad de Alicante, Apdo. 99, E-03080, Alicante, Spain

*Corresponding author.

Abstract

This review covers the recent developments (since 2015) of enantioselective desymmetrization reactions using metal-catalyzed, organocatalyzed and enzymatic processes of prochiral and *meso*-compounds. This asymmetric strategy has been applied to a great number of organic complunds such as diarylalkanes, silanes, alcohols, amines and dibenzylmethylamines, as well as unsaturated compounds comprising dienes, diynes and cyclohexenes. The classical desymmetrization of 1,2-, 1,3-diols and other polyols by inter- and intramolecular acylation and alkylation reactions, but also by oxidation methods are important processes. Carbonyl compounds such as cycloalkanones, cyclohexadienones, cyclic and acyclic 1,3-diketones, cyclic 1,4-diketones are desymmetrized and applied to the synthesis of a wide range of natural products. In the case of dicarboxylic acid derivatives, diesters and lactones, anhydrides, diamide and dinitriles are mainly desymmetrized by intra- and intermolecular esterifications and hydrolysis. Small ring carbocycles such as cyclopropanes and cyclopropenes, cyclobutanes and cyclobutenes, and also cyclopentanes and cyclopentenes, cyclohexanes and cyclohexenes are considered. Heterocyclic systems such as small ring oxygen containing epoxides, oxetanes and oxabenzonorbornadienes as well as nitrogen containing aziridines, azetidines, azabenzonorbornadienes and diazanorbornenes are desymmetrized mainly by asymmetric ring opening reactions. The synthetic applications of these desymmetrization methodologies in the total synthesis of natural products and biologically active compounds are highlighted.

Keywords:

Desymmetrization, *meso*-Compounds, Organocatalysis, Metal-catalysis, Biocatalysis

Abbreviations

No keyword abbreviations are available

Abreviations

AAS Asymmetric allylic substitution

Ac Acetyl

ACAAC Azide-alkyne cycloaddition

ACE Angiotensin converting enzyme

AJ270 *Rhodococcus erythropolis*

AKU4429 *Sporobolomyces salmonicolor*

An-SDP
[4′-Bis-(4-methoxyphenyl)phosphanyl-3,3′-spirobi-[1,2-dihydroindene]-4-yl]-bis-(4-methoxyphenyl)phosphane

Ar Aryl(s), argon

ARO Asymmetric ring opening

atm Atmosphere

B_2pin_2 Bis(pinacolato)diboron

BCL *Burkholderia cepacia*

BDPP 1,3-Dimethyl-1,3-(diphenylphosphine)propane

BINAP 2,2′-Bis(diphenylphosphino)-1,1′-binaphthyl

BINOL 11′-Bi-2-naphthol

BINOLAM 2,2‘-Bis(diethylaminomethyl)binaphthol

BMIM 1-Butyl-3-methylimidazolium

Bn Benzyl

Boc *tert*-Butoxycarbonyl

BOPP 1,3-Dimethyl-1,3-bis(diphenylphosphino)propane

Box Bisoxazoline

(*R,R*)-BozPhos 1,2-Bis-[(2*S*,5*S*)-2,5-dimethylphospholano]benzene

Bz Benzoyl

CAL-A *Candida antartica* lipase

cat Catalyst

Cbz Benzyloxycarbonyl

cod 1,5-Cyclooctadiene

COE Cyclooctene

Cp Cyclopentadienyl

Cp* Pentamethylcyclopentadienyl

CPA Chiral phosphoric acid

Cy Cyclohexyl

DABCO Diazabicyclo[2.2.2]octane

DACH-phenyl 1,2-Diaminocyclohexane-*N*,*N*′-bis-(2-diphenylphosphinobenzoyl)

dba Dibenzylideneacetone

dbcot Dibenzocyclooctatetraene

DBU 1,8-Diazabicyclo[5.4.0]undec-7-ene

DCDMH Dichlorodimethylhydantoin

DCE 1,2-Dichloroethane

DPEN (1*R*,2*R*)-Diphenylethylenediamine

DFT Density functional theory

$(DHQD)_2PHAL$ Hydroquinidine 1,4-phthalazinedyl diether

(*S*)-Difluorphos (*S*)-5,5-Bis(diphenylphosphino)-2,2,2’,2′-tetrafluoro-4,4′-bi-1,3-benzodioxole

DIPEA Diisopropylethylamine

DKR Dynamic kinetic resolution

DMA *N,N*-Dimethylacetamide

DMAP 4-Dimethylaminopyridine

DMDO Dimethyldioxirane

DME 1,2-Dimethoxyethane

DMF Dimethylformamide

DM-Segphos 5,5′-Bis[di(3.5-xylyl)phosphino]-4,4′-bi-1,3-benzodioxole

DMSO Dimethylsulfoxide

DPEN 1,2-Diphenyl-1,2-ethanediamine

dr Diastereomeric ratio

DSM *Rhondonoccus erythropolis* cells

DTBM-MeOBIPHEN 6,6′-Dimethoxybiphenyl-2,2′-diyl)bis(diphenylphosphine)

DTBMP 2,6-Di-*tert*-butyl-4-methylpyridine

DTBM-Segphos 4,4′-Bis-(1,3-benzodioxole)-5,5′-diylbis(diphenylphosphine)

ECS-PLEO6 Fed-batch manner enzyme

ee Enantiomeric excess

equiv Equivalent(s)

er Enantiomeric ratio

ET Electron transfer

FAD Flavin adenine dinucleotide

FC Friedel-Crafts

FDH Flavoin-dependent helogenase

ferriphos 1,1′-Bis-(1-methylaminoethyl)-2,2′-bis(diphenylphosphino)ferrocene

Foxap (*S*)-1-(Diphenylphosphino)-2-[(*S*)-4-*tert*-butyloxazolin-2-yl]ferrocene

FR901483 Immunosuppressant

GABAA γ-Aminobutyric acid

Glu Glucose

HAT Hydrogen atom transfer

HESPES 4-(2-Hydroxyethyl)piperazin-1-ethanesulfonic acid

HFIP Hexafluoroisopropanol

HIV Human immunodeficiency virus

HPESW Hajos-Parrish-Eder-Sauer-Wiechert

IBX 2-Iodoxybenzoic acid

(*R,S*)-Josiphos (*R*)-1-[(S_p)-2-(diphenylphosphino)ferrocenyl)ethyldicyclohexylphosphine

L Ligand

LED Light emitting diode

LEH Limonene epoxide hydrolase

Leu Leucine

M Metal

MBP Maltase binding protein

MCPBA *meta*-Chloroperbenzoic acid

MeOBiphep 6,6-Dimethoxy-2,2′-diphenyldiphenyl

Mes Mesityl

Me-THF 2-Methyltetrahydrofuran

MIM Acetobacter aceti

MS Molecular sieves

MTBE Methyl *tert*-butyl ether

MW Microwaves

NaBARF Sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate

NADH Nicotinamide adenine dinucleotide

$NADP^+$ Nicotonamide adenine dinucleotide phosphate

NBCR10231 *Candida cacacoi*

NBCR102419 *Eschericia fergusonii*

NBCR10896 *Pichia farinosi*

NBCR13501 *Providencia rettgeri*

NBCR3168 *Marganella morganti*

NBD Norbornadiene

nbd Norbornadiene

NBE Norbornene

NBS *N*-Bromosuccinimide

NHC N-Heterocyclic carbene

NMP *N*-Methylpyrrolidone

Novozym 435 *Candida antartica* inmobilized

NPSP *N*-(Phenylamino)phthalimide

Ns 4-Nitrobenzenesulfonyl

P450 BM3 F87ACytochrome

PCCP Pentacarbonylcyclopentadiene

PFL *Pseudomonas fluorescens*

PG Protecting group

PGF2a Vaginal prostaglandine

(*S*)-Ph-BPE 1,2-Bis-[(2*S*,5*S*)-2,5-diphenylphospholano)ethane

Phen 1,10-Phenanthroline

PhthN Phthalimino

PIB *para*-Iodobenzyl

PLE Porcine liver stearase

PMB *para*-Methoxybenzyl

PMP *para*-Methoxyphenyl

PPF-P*t*Bu$_2$ [Bis-(1,1-dimethylethyl)phosphino]ethyl]-2-(diphenylphosphino)ferrocene

PPL Porcine pancreas lipase

Phanephos 4,12-Bis(diphenylphosphino)paracyclophan

Pro Proline

PS Phosphatidylserine synthase

psi Pounds per square inch

PT Proton transfer

Py Pyridyl

Pybox 2,6-Dioxazolinepyridine

Pyrabox 2,5-Bis-(3-*tert*-butyloxazinyl)diazine

Ras *Ralstonia* sp.

RCM Ring closing metathesis

RebH Rebecamycin halogenase

RM-IM Lipozime

rt Room temperature

RuPhos 2-Dicyclohexylphosphino-2′,6′-diisopropoxybiphenyl

SCN-80 Opioid receptor agonist

S Sulfphur, solvent

SET Single electron transfer

SPINOL 1,1′-Spirobiindan-7,7′-diol

TADDOL α,α,α′,α′-Tetraaryl-2,2-disubstituted 1,3-dioxolane-4,5-dimethanol

TBAB Tetrabutylammonium bromide

TBDPS *tert*-Butyldiphenylsilyl

TBME *tert*-Butyl methyl ether

t-BuPhox 4-*tert*-Butyl-2-[2-(diphenylphosphino)phenyl]-2-oxazoline

TCPTTL Tetrachlorophthaloyl-*tert*-leucinate

Tf Triflic

TFA Trifluoroacetic acid, trifluoroacetate

THF Tetrahydrofuran

TL-IM Lipozime

TmCHMO Thermostable Baeyer-Villiger monoxygenase

TMEDA Tetramethylethylenediamine

TMP 2,2,6,6-Tetramethylpiperidine

TMS Trimethylsilyl

TRIP 3,3′-Bis-(2,4,6-triisopropylphenyl)-1,1′-binaphthol cyclic monophosphate

Ts Tosyl

TS Transition state

TsDPEN *N*-Tosyl-1,2-diphenyl-1,2-ethylenediamine

Val Valine

VPC01091 Sphingosine receptor

Xantphos 4,5-Bis(diphenylphosphino)-9,9-dimethylxantene

Xyl-BINAP 2,2′-Bis[di(3,5-xylyl)phosphino]-1,1′-binaphthyl

Xyl-SPD

[4′-Bis-(3,5-dimethylphenyl)phosphanyl-3,3′-spirobi[1,2-dihydroindene]-4-yl]-bis(3,5-dimethylphenyl)phosphane

xylene Dimethylbenzene

Yanphos Chiral (binaphthyl)derived ligand

1 Introduction

Desymmetrization has become one of the most important, elegant and powerful strategies in asymmetric synthesis in the last 20 years. Enantioenriched molecules can be prepared from achiral or *meso* starting molecules by using metal catalysis, organocatalysis and enzymes. Since 1999 [1] several reviews have been published on this subject mainly focused on substrates but also on catalysts [2–26]. This methodology has been used for the generation of chiral molecules with complex structures including many natural products [9,15,17,20]. Since the publication of the most recent general reviews covering until 2015 [13,14] numerous advances in this field have been achieved. In this review a comprehensive survey on catalyzed desymmetrization reactions of different types of compounds, such as *gem*-disubstituted methanes, acyclic and cyclic dienes, diynes, diols, ketones, cyclohexadienones and diketones, dicarboxylic acid derivatives, functionalized carbocyclic compounds and saturated heterocycles will be presented.

2 Desymmetrization of *gem*-disubstituted methanes

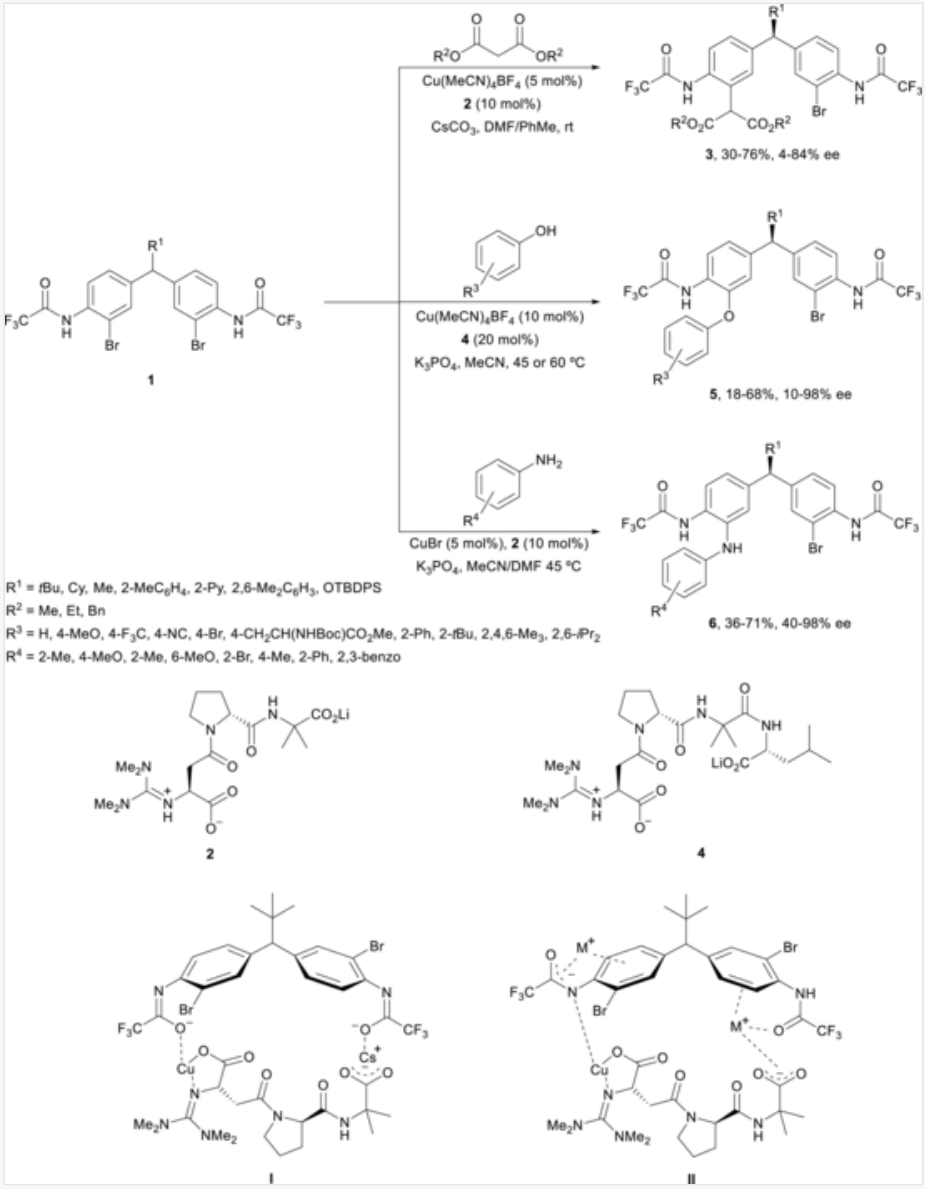
In this Section 2, symmetry-breaking reactions of diarylmethanes, diarylmethylalcohols and silanols, diarylmethylamines and dibenzylmethylamines will be considered.

2.1 Diarylmethanes

Chiral enantioenriched diarylmethanes are privileged scaffolds in drug discovery~~disvovery~~ [22]. Remote desymmetrization of diarylmethanes has been performed by Miller and co-workers using peptides as chiral ligands [23, 26]. Recently, they described a copper-catalyzed Ullman cross-coupling reaction using chiral guanidines as ligands affording high levels of enantiocontrol in the case of substrates **1** and dialkyl malonates (Scheme 1) [27]. These aryl bromides **1** were smoothly alkylated at room temperature using the catalyst derived from $Cu(MeCN)_4BF_4$ and ligand **2**. With respect to the nucleophile, the highest yields for products **3** were obtained with unsubstituted malonates. In the case of different diarylmethanes, the *tert*-butyl group gave the best results (up to 92:8 er), whereas decreasing steric size led to lower selectivity. Mechanistic studies supported that this long range asymmetric induction can be achieved by the dimensions of the catalyst. The presence of Cs ions bridged the C−terminal carboxylate with the deprotonated amide in model **I** (right part). In the other Cu C−terminal carboxylate (left part) of model **I**, the other deprotonated amide would be coordinated.

alt-text: Scheme 1

Scheme 1



Desymmetrization of diarylmethanes **1** by an enantioselective Ullman cross-coupling with malonates, phenols and anilines.

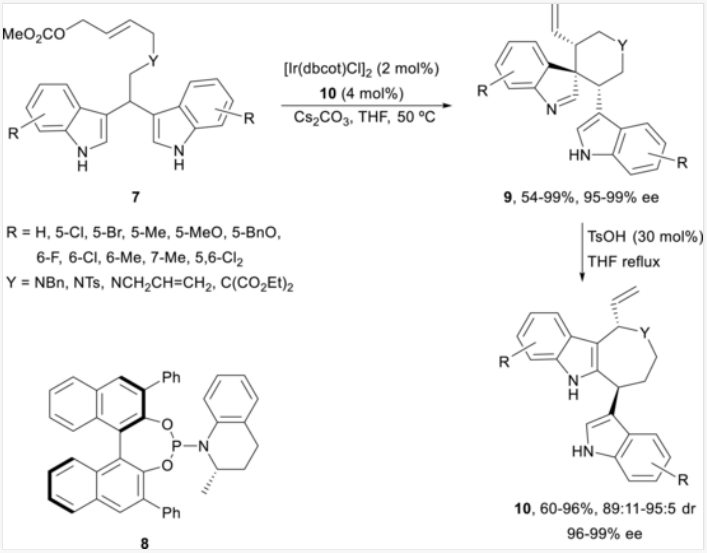
The same group [28] has performed the desymmetrization of compounds of the type **1** under Cu-catalyzed cross-coupling with phenols as nucleophiles. In this case, the peptide-based ligand **4** gave the best results affording mainly products **5** in good yields and up to 98% ee (Scheme 1). Only electron-poor phenols were less reactive and allyl alcohol gave only 13% of the coupled product in >99:1 er. However, benzyl alcohol reacted at 60 °C providing the corresponding product in 43% yield whereas 4-hydroxybenzyl alcohol reacted at 60 °C preferentially by the phenolic oxygen to provide the expected product in 65% and 96:4 er. Similarly, 5-hydroxyindole gave chemoselectively the C–O bond forming cross-coupling reaction. Sterically hindered phenols, which remained challenging for Cu-catalyzed cross-coupling reactions, gave moderate to good yields (33–50%). Concerning diarylmethane scope, the *tert*-butyl derivative gave the highest yields and enantioselectivities. Also in this case, in the proposed interactions between the catalyst **4** and the substrate are represented in intermediate **II**. The effect of peptide length has been demonstrated using different guanidinylated ligands. Enantioselective C–N bond forming reactions have been carried out with aromatic primary amines using CuBr (5 mol%) and ligand **2** (10 mol%) giving the corresponding products **6** in moderate to good yields and moderate to high enantioselectivities [29]. The resulting products **6** were further cyclized using a chiral phosphoric acid to the corresponding atropoisomeric benzimidazoles.

You and co-workers [30,31] have performed a desymmetrization strategy based on iridium-catalyzed allylic dearomatization reactions. Spiroindolenines **9** were prepared in high yields and enantioselectivities starting from bisindolylmethane compounds **7** bearing an allylic carbonate [30] (Scheme 2). This allylic unit trigged the intramolecular allylic substitution catalyzed by IrCldibenzocyclooctatetraeno (dbcot) complex (2 mol%) and phosphoramidite **8** as a achiral ligand to provide the chiral spiroindolenines **9**. These compounds have been further

submitted to ring expansion in acidic medium leading to hexahydroazepino[4,5-*b*]indoles **10**. Compounds **10** are closely related to some natural products such as trigolutesins, trigolute B and malassezindole A.

alt-text: Scheme 2

Scheme 2

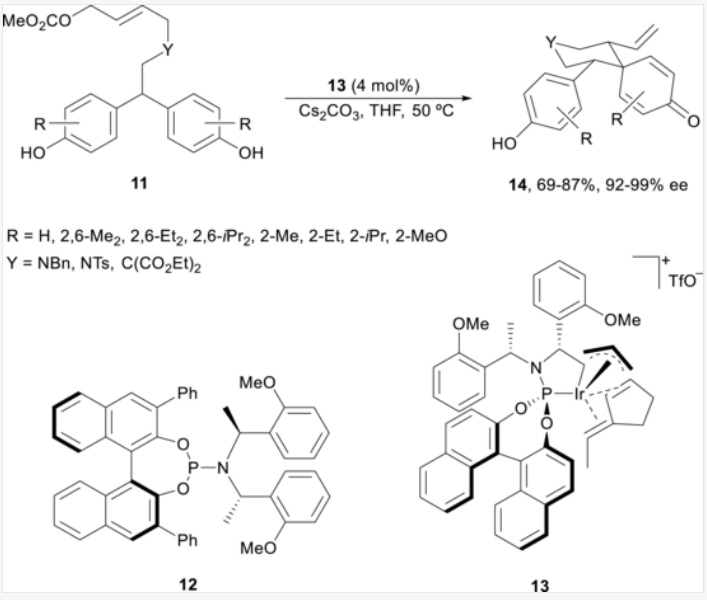


Desymmetrization of bisindolylmethanes **7** by an enantioselective Ir-catalyzed allylic dearomatization.

In the case of bisphenolmethanes **11**, the corresponding desymmetrization took also place by intramolecular Ir-catalyzed allylic substitution (Scheme 3) [31]. The best results were achieved using the cyclometalated Ir-complex **13** derived from phosphoramidite **12** giving single diastereomers **14** in good yields and high enantiomeric ratios. One of these spirocyclic hexadienones with multiple stereocenters has been applied to the total synthesis of (+)-tatanan B and C, natural products isolated from the rhizomes of *Acorus tatarinowii*, which display antidiabetic activity.

alt-text: Scheme 3

Scheme 3

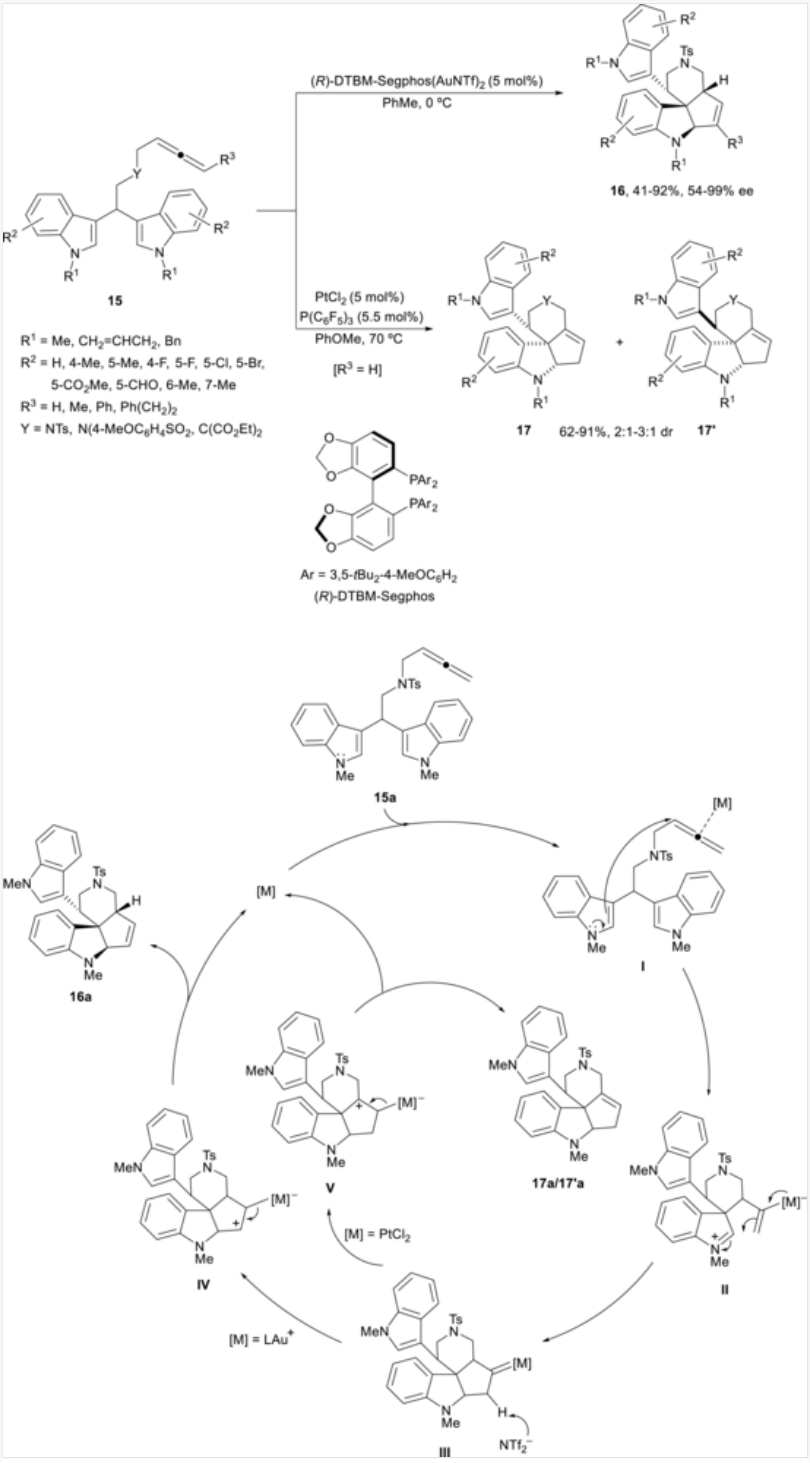


Desymmetrization of bisphenolmethanes **11** by an enantioselective Ir-catalyzed allylic dearomatization.

Bisindolylmethanes bearing an allene unit **15** underwent intramolecular cycloadditions under catalyst control [32]. Two different types of fused spiroindolines can be obtained regiodivergently [33] using Au(I) and $PtCl_2$ as metal catalysts. The Au(I)-catalyzed cycloaddition reaction gave spiroindoline derivatives **16** in good yields and excellent regioselectivities. On the other hand, under $PtCl_2$ catalysis the intramolecular cycloaddition provided fused spiroindolines **17** and **17′** in moderate diastereoselectivities. The asymmetric desymmetrization took place using the Au(I) complex with chiral ligands. The highest enantioselectivities were obtained using (*R*)-DTBM-Segphos at 0 °C giving the spiroindolines **16** in good yields and enantioselectivities (Scheme 5). Both cycloadditions took place according to experimental and DFT calculations as it is depicted in Scheme 4. Intermediate **I** is generated by coordination of Au(I) or $PtCl_2$ with the allene moiety in compound **15a**, which after nucleophilic attack at C3 position resulted intermediate **II**. By intramolecular cyclization of intermediate **II** the common carbenoid intermediate **III** will be formed, which by a [1,2]-proton transfer resulted intermediates **IV** and **V**. Final release of Au(I) or $PtCl_2$ produces the cycloaddition products **16a** or **17a**/**17′a**, respectively.

alt-text: Scheme 4

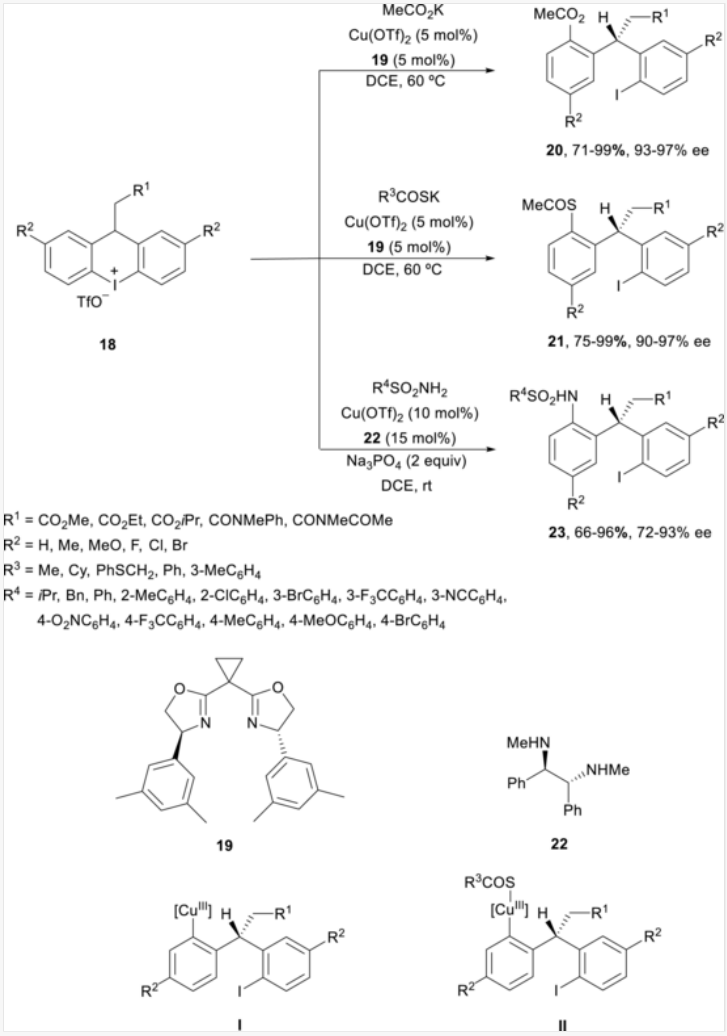
Scheme 4



Desymmetrization of bis(indol-3-yl)allenes **15** under Au(I) and Pt(II) catalyzed enantioselective cycloaddition.

alt-text: Scheme 5

Scheme 5



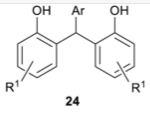
Cu-Catalyzed desymmetrization of cyclic diaryliodonium salts **18**.

Copper-catalyzed desymmetrizations of cyclic diaryliodonium salts **18** have been described using carboxylic acids or thioacids [34] and sulfonamides [35] as nucleophiles (Scheme 5). Enantioselective ring opening of six-membered cyclic diaryliodonium salts afforded chiral diarylmethanes in the presence of cyclopropyl bis(oxazoline) **19** as ligands to give products **20** in the case of carboxylates and **21** with thiocarboxylates in excellent yields and enantioselectivities [34]. The Cu(I)ligand is the active catalyst, which underwent oxidative addition with **18** to form intermediate **I**. Subsequent coordination of the potassium thioate to the Cu(III) center gave **II**, which would give the final product **21** *via* reductive elimination. The observed stereochemistry was explained by the depicted **TS** in which the steric repulsion between the alkyl chain (CH_2CO_2Et) and the bisoxazoline is minimized. In the case of sulfonamides, diamine **22** was used as a chiral ligand giving products **23** at room temperature with up to 93% ee [35].

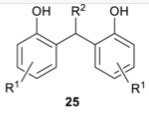
Triarylmethanes **24** and 1,1-diarylalkanes **25** have been desymmetrized by N-heterocyclic carbene(NHC)-catalyzed acylation of bisphenols [36]. The enantioselective acylation of compounds **24** and **25** was carried out with aldehydes and the chiral NHC resulting from **26** at room temperature giving products **27** and **28**, respectively, in good yields and ee's (Scheme 6). DFT calculations reveals that the selectivity is governed by the C–C bond cleavage step of the tetrahedral **TSI**. Bis(phenols) are important scaffolds in many biological and pharmaceutical compounds [37]. Chen and Li group further described a similar methodology for the desymmetrization of 1,1-diarylalkanes **25** using the same NCH derived from **26** (Scheme 6) [38]. In this case, several aromatic and aliphatic aldehydes in the presence of quinone as the oxidant gave the corresponding products in good yields and enantioselectivities. Based on linear free energy relationship analysis and both steric and electronic effects **TSII** was proposed.

alt-text: Scheme 6

Scheme 6



24

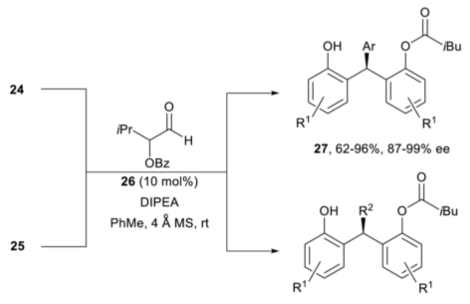


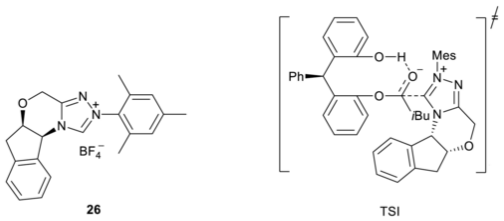
25

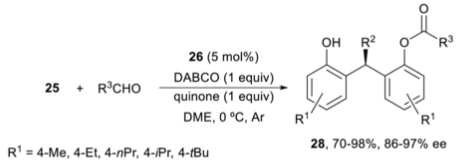
Ar = Ph, 4-MeC_6H_4, 4-*i*PrC_6H_4, 4-*t*BuC_6H_4, 4-PhC_6H_4, 4-ClC_6H_4, 4-FC_6H_4, 2-MeC_6H_4, 2-naphthyl, 2-furyl

R^2 = Me, *t*Bu, *n*C_6H_{13}, $(CH_2)_6OH$

R^1 = H, 4-Me, 4-*t*Bu, 4-MeO, 4-Cl, 3-Me, 3-*t*Bu, 3-F, 3,4-(OCH_2O)



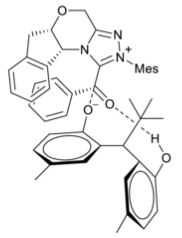




R^1 = 4-Me, 4-Et, 4-*n*Pr, 4-*i*Pr, 4-*t*Bu

R^2 = *t*Bu, *i*Pr, Cy, 1-adamantyl

R^3 = Ph, 2-FC_6H_4, 2-ClC_6H_4, 2-BrC_6H_4, 2-IC_6H_4, 2-MeC_6H_4, 2-$F_3C$$C_6H_4$, 3-$O_2N$$C_6H_4$, 3-F$C_6H_4$, 3-Me$C_6H_4$, 3-MeO$C_6H_4$, 4-$O_2N$$C_6H_4$, 4-F$C_6H_4$, 4-Me$C_6H_4$, 4-MeO$C_6H_4$, 4-$F_3C$$C_6H_4$, 4-$F_3CO$$C_6H_4$, 4-NC$C_6H_4$, 4-Ph$C_6H_4$, 2-Br-5-F$C_6H_3$, 1-naphthyl, 2-furyl, 2-thienyl, 2-styryl, Et, *i*Pr



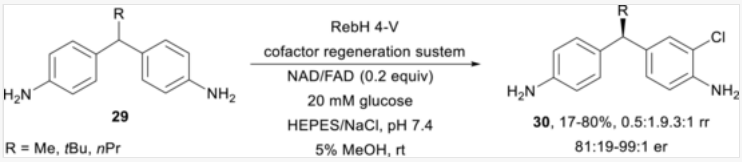
TSII

NHC-Catalyzed desymmetrization of bisphenols **24** and **25** by an enantioselective acylation.

4 V~~V~~ Variants of rebecamycin halogenase (RebH) catalyzed the enantioselective desymmetrization of 1,1-diarylalkanes **29** bearing amino groups at the *para* position [39]. This remote monochlorination at the 3-position takes place with good regioselectivity and enantioselectivity providing products **30** (Scheme 7). These Flavin-dependent halogenases (FDHs) with improved stability were substituted by protein engineering by Lewis and co-workers [39] based on docking simulations. The enzymatic desymmetrization was carried out using 0.5 mol% of maltase binding protein MPB-RebF and 50U/mL glucose dehydrogenase and 0.2 equivalents of nicotinamide adenine dinucleotide (NAD) and in 10 mg scale.

alt-text: Scheme 7

Scheme 7



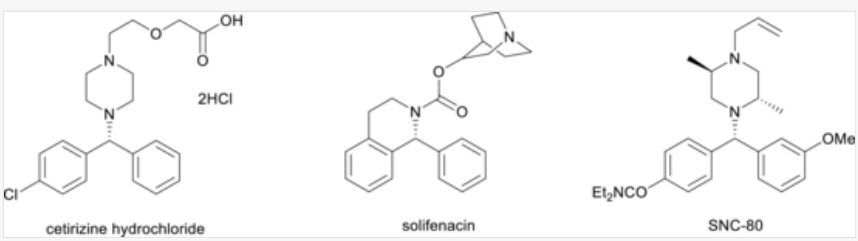
Enzymatic desymmetrization of 1,1-diarylalkanes **29** by an enantioselective chlorination.

2.2 Diarylmethylamines

Optically active diarylmethylamines are key constituents in pharmacological active compounds such as the antihistamine cetirizine hydrochloride [40], solifenacin used in the treatment of urinary incontinency [41] and the δ opioid receptor agonist SCN-80 [42] (Fig. 1). One of the most useful strategy for the enantioselective preparation of these amines are metal-catalyzed desymmetrization processes, based on intra- and intermolecular C–H functionalization reactions.

alt-text: Fig. 1

Fig. 1

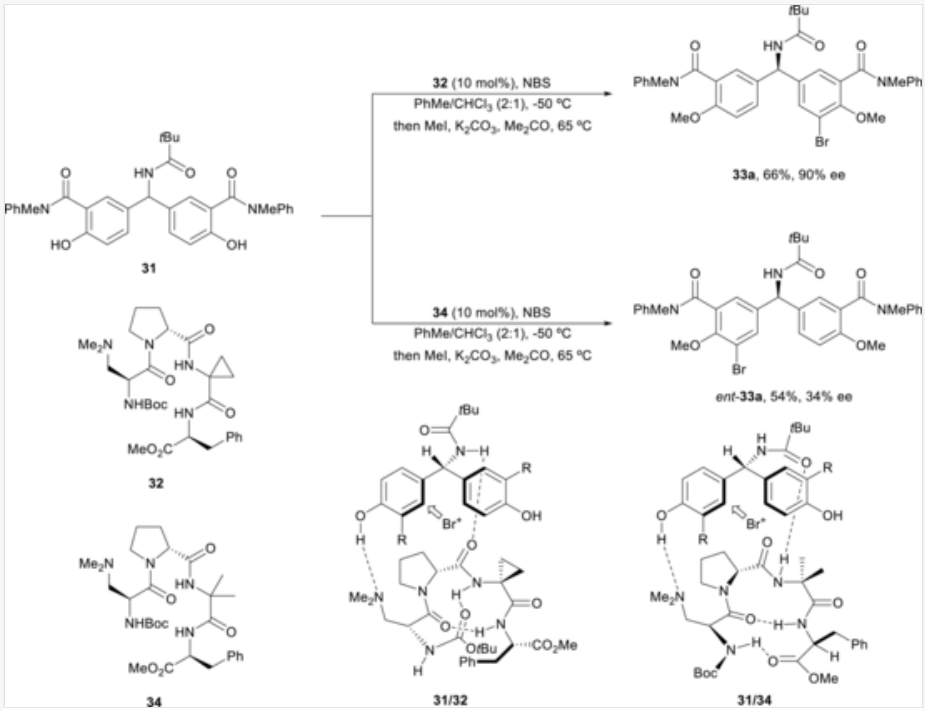


Optically active bioactive diarylmethylamines.

Miller and co-workers [43] applied the peptide-base catalysis [23,26] to the electrophilic aromatic bromination with NBS of diarylmethylamido bis(phenols) **31**. Interestingly, they found out a catalyst-dependent enantodivergence [44] during the desymmetrization of compound **31**. When catalyst **32** was used product **33a** was obtained in 90% ee after methylation, whereas using catalyst **34** under the same reaction conditions *ent*-**33a** was isolated in moderate yield (34%) (Scheme 8). Using catalysts **32** and **34** several substrates with different amide units were brominated mainly to products of type **33** in 49–66%. Based on structural analysis it was deduced that **32** adopts prehelical β-turn structure and **34** exists in β-hairpin conformation, and the proposed models how these catalysts interact with the substrate **31** are presented in Scheme 8. In both models **31/32** and **31/34** a key intermolecular hydrogen bond between the tertiary amine of the catalyst and the OH of the phenol moiety activates the substrate toward S_EAr. The binding orientation in both cases is therefore antipode with respect to the central pivalamide.

alt-text: Scheme 8

Scheme 8

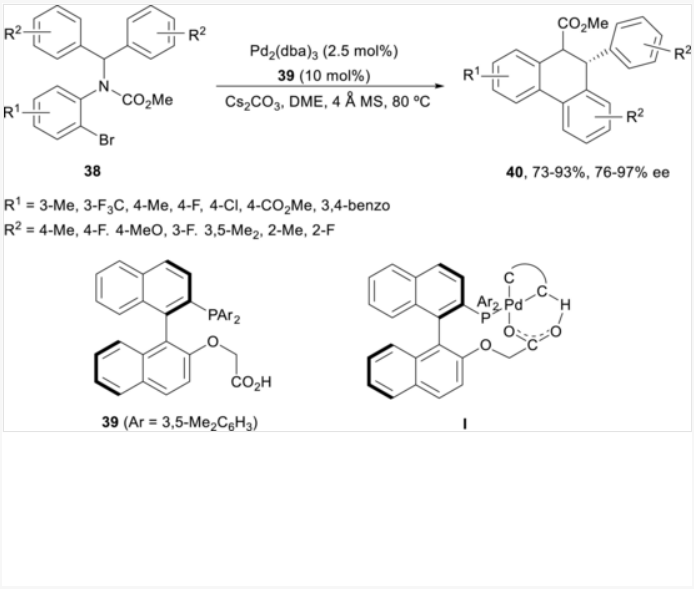


Peptide-catalyzed desymmetrization of diarylmethylamido bis(phenols) **31** by an enantioselective bromination.

Metal-catalyzed enantioselective C–H functionalizations has become a powerful strategy for desymmetrization reactions of diarylmethylamines. Grosheva and Cramer [45] reported a Pd-catalyzed C–H functionalization diarylmethylamino derivatives **35** bearing a ketene aminal phosphate unit. In the presence of monodentate chiral phosphine **36** as ligand an enantioselective intramolecular arylation took place at room temperature, through palladacycle **I**, giving isoindoline derivatives **37** in good yields and enantioselectivities (Scheme 9).

alt-text: Scheme 9

Scheme 9

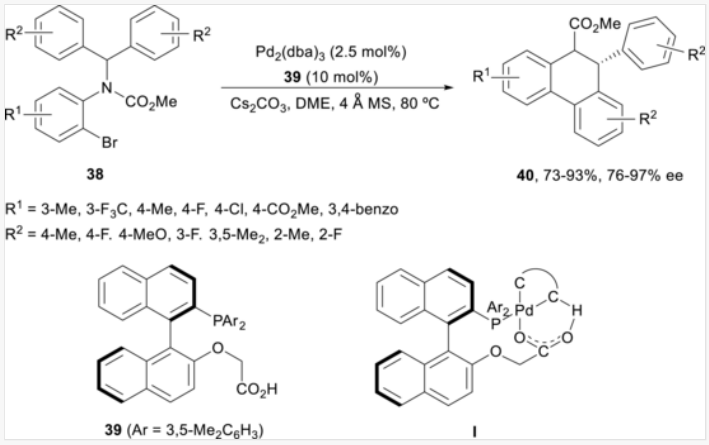


Pd-Catalyzed desymmetrization of diarylmethylamines **35** by an enantioselective C–H functionalization.

Enantioselective intramolecular Pd-catalyzed C–H arylation was performed with carbamates derived from diarylmethylanilines **38** using a bifunctional chiral phosphine/carboxylate **39** as ligand (Scheme 10) [46]. The resulting 5,6-dihydrophenanthridines **43** were obtained in good yields and enantioselectivities. In contrast, the corresponding monofunctional ligands, lacking a carboxylic acid function induced low enantioselectivities. Consequently, the proposed mechanism proceeds *via* an ambiphilic metal ligand activation presented in model **I** (Scheme 10). Concerning the substrates **38** bromo-substituted anilines gave higher yields than chloro, iodo and triflate derivatives. With respect to the nitrogen substituent, the best results were obtained using alkoxycarbonyl groups better than sulfonamides or trifluoroacetamides.

alt-text: Scheme 10

Scheme 10

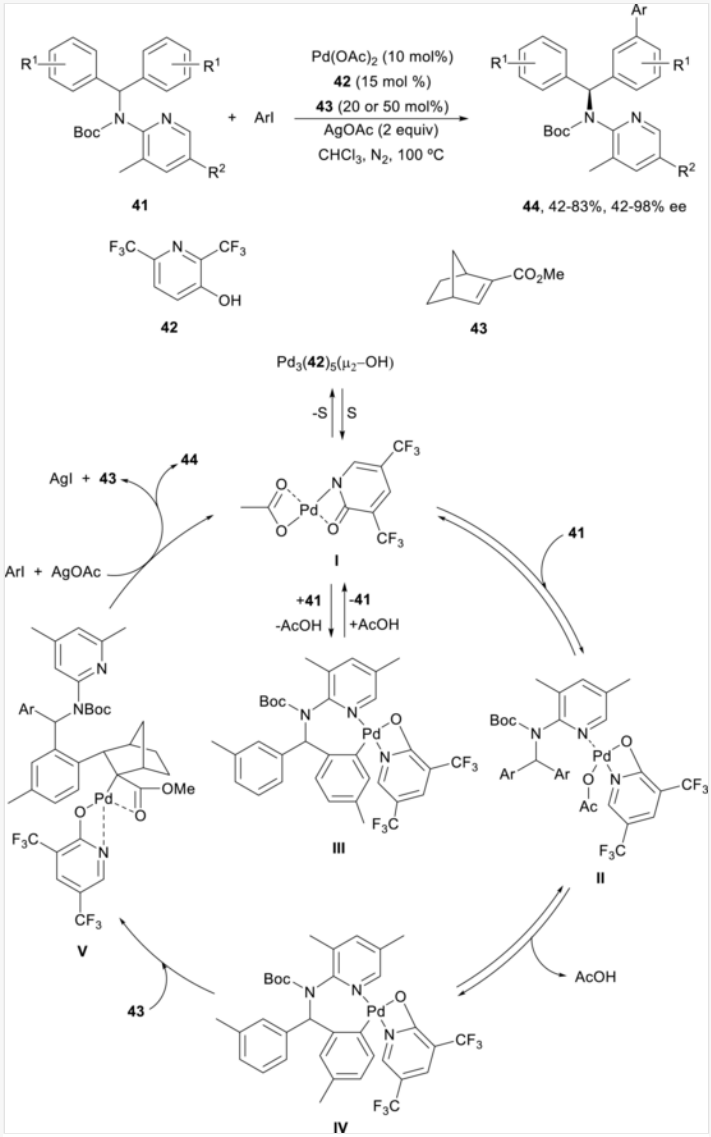


Pd-Catalyzed desymmerization of diarylmethylamines **38** by an intramolecular enantioselective C–H arylation.

Yu and co-workers [47] developed an enantioselective remote *meta*-C–H arylation for the desymmetrization of diarylmethylamine derivatives **41** (Scheme 11). This Pd-catalyzed C–H functionalization is accelerated by a pyridone ligand **42** and enhancing the enantio-determining insertion of an arylpalladium species into a chiral norbornene derivative **43** [48]. Under these reaction conditions *m*-arylated diarylmethylamines **44** bearing a 2-pyridyl substituent at the nitrogen atom were obtained in moderate to good yields and enantioselectivities. Different aromatic as well as heteroaromatic iodides were used leading to a general arylation process. Observations from kinetic analysis monitorized by ^{19}F NMR supported a reaction mechanism depicted in Scheme 11 [45]. The pyridone ligand **42** aids in breaking up the Pd trimer to form the active catalytic species **I** which reacts reversibly with **41** to form intermediates **II** and **III**. After *o*-palladation to form **IV**, this complex undergoes rate-determining 1,2-migratory insertion into norbornene **43** giving intermediate **V**. Final oxidative addition of the aryl iodide yielded product **44**.

alt-text: Scheme 11

Scheme 11

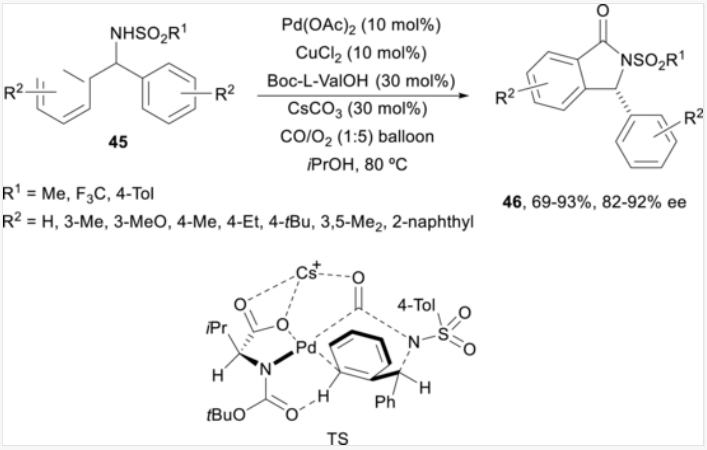

Pd(OAc)2 (10 mol%)
42 (15 mol %)
43 (20 or 50 mol%)
AgOAc (2 equiv)
CHCl3, N2, 100 °C
41
44, 42-83%, 42-98% ee
42
43
Pd3(42)5(μ2–OH)
-S
S
AgI + 43
44
ArI + AgOAc
I
41
+41
-AcOH
-41
+AcOH
III
II
V
43
AcOH
IV

Pd-Catalyzed desymmetrization of diarylmethylamine **41** by an intermolecular enantioselective C–H arylation.

Asymmetric carbonylation of sulfonamides derived from diarylmethylamines **45** has been carried out by Xu and co-workers [49]. The enantioselective C–H carbonylation took place using a Pd/Cu catalyst and Boc-L-ValOH as a chiral ligand with a CO/with a CO/O_2 balloon at 80 °C to afford isoindolin-1-ones **46** (Scheme 12). According to DFT calculations a plausible enantioselective carbamoyl-Pd oriented C–H instead of the amine-derived C–H activation mechanism was proposed. Transition state **TS**, in which activated C–H bond was oriented blow the Pd coordination plane, has the lowest free energy giving the (*R*)-enantiomer.

alt-text: Scheme 12

Scheme 12

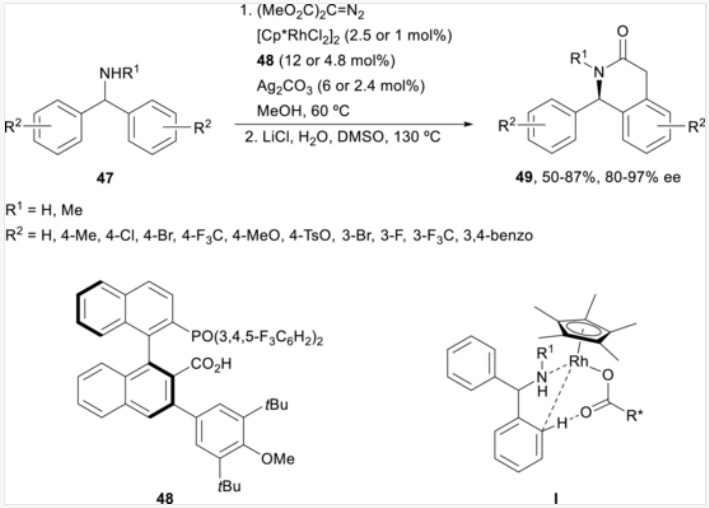


Pd/Cu-Catalyzed desymmetrization of sulfonamides derived from diarylmethylamines **45** by an enantioselective C–H carbonylation reaction.

A Rh(III)-catalyzed C–H alkylation with diazomalonate has been applied to the desymmetrization of dietylmethylamines **47** using a chiral carboxylic acid **48** (Scheme 13) [50]. After concerted metalation-deprotonation, the alkylation with diazomalonate took place followed by cyclization and decarboxylation with LiCl in DMSO at 130 °C to afford 1,4-dihydroisoquinolin-3(2*H*)-ones **49** in high yields and enantioselectivities. A possible intermediate **I** between the diarylmethylamine and the Cp*Rh(III)/R*CO_2H catalyst has been postulated.

alt-text: Scheme 13

Scheme 13

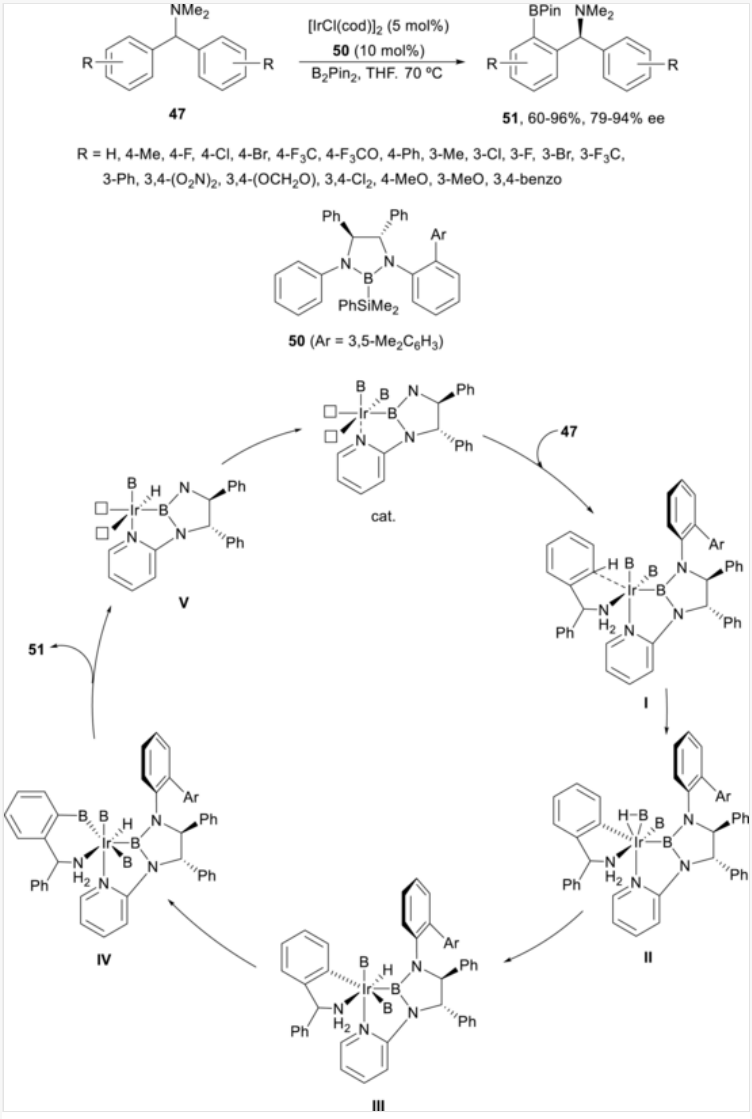


Rh-Catalyzed desymmetrization of diarylmethylamines **47** by an enantioselective C–H alkylation with diazomalonate using a chiral carboxylic acid **48**.

Ke, Xu and co-workers [51] reported an Ir-catalyzed asymmetric C–H borylation of diarylmethylamines **47** using a chiral bidentate boryl ligand **50**. This new type of ligands derived from (*S,S*)-1,2-diphenyl-1,2-ethanediamine [(*S,S*)-DPEN] were prepared by reaction of the diamine with $PhMe_2SiB(NiPr_2)_2$ in the presence of a catalytic amount of HCl at 180 °C. Ligand **50** gave the best yield and enantioselectivity in the borylation of amines **47** with B_2pin_2 to furnish products **51** (Scheme 14). From substrate structures studies it was found that compounds **47** with a dimethylamine unit worked better than dietylamine, pyrrolidines, piperidine and morpholine, probably due to steric hindrance preventing coordination of the N atom with the Ir center. The proposed reaction mechanism is based on DFT calculations with a simplified Ir-boryl catalyst. In the proposed catalytic cycle three major steps are considered: after coordination of the amine to the catalyst giving intermediate **I** a C–H oxidative addition provided intermediate **II**, which isomerizes to **III**. The, the C–B bond formation occurred to generate intermediate **IV**, which evolved to form the product and the catalytic species. From these theoretical results it was concluded that the C–H bond activation is the rate-determining step, which also led to the enantioselectivity of the borylation.

alt-text: Scheme 14

Scheme 14

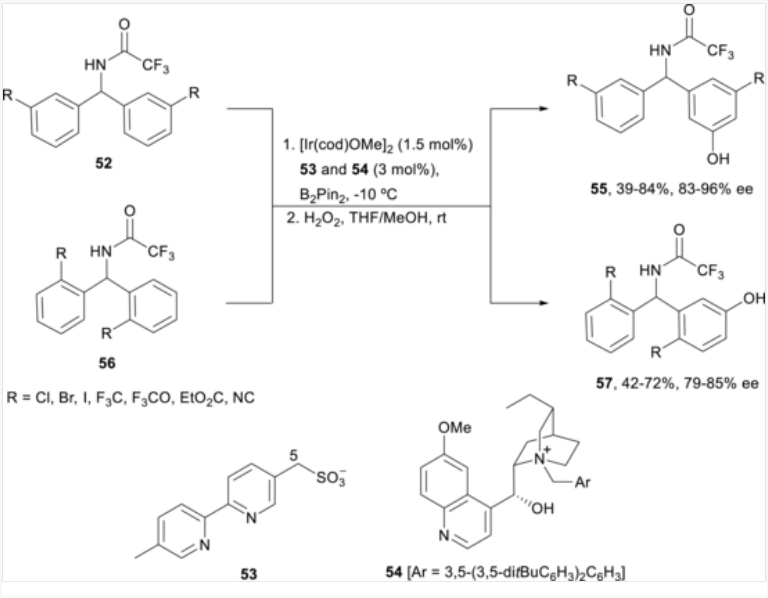


Ir-Catalyzed desymmetrization of diarylmethylamines **47** by an enantioselective C–H borylation.

Recently, Genov and co-workers [52] performed an enantioselective remote C–H activation of diarylmethylamides **52** by Ir-catalyzed borylation using an anionic ligand **53** and a chiral cation **54** (Scheme 15). The reaction takes place at room temperature with only 3 mol% of catalyst giving after oxidation of the borylated products at the *meta*-position hydroxylated products **55**. This catalyst not only control the enantioselectivity but also the regioselectivity. In the case of *meta*-substituted diarylmethylamides **52** product **55** were obtained whereas *ortho*-substituted benzhydrylamides **56** gave products **57**. Intermediate **I**, with the chiral cation **54** blocking the back face of the substrate can explain the observed enantioselectivity.

alt-text: Scheme 15

Scheme 15

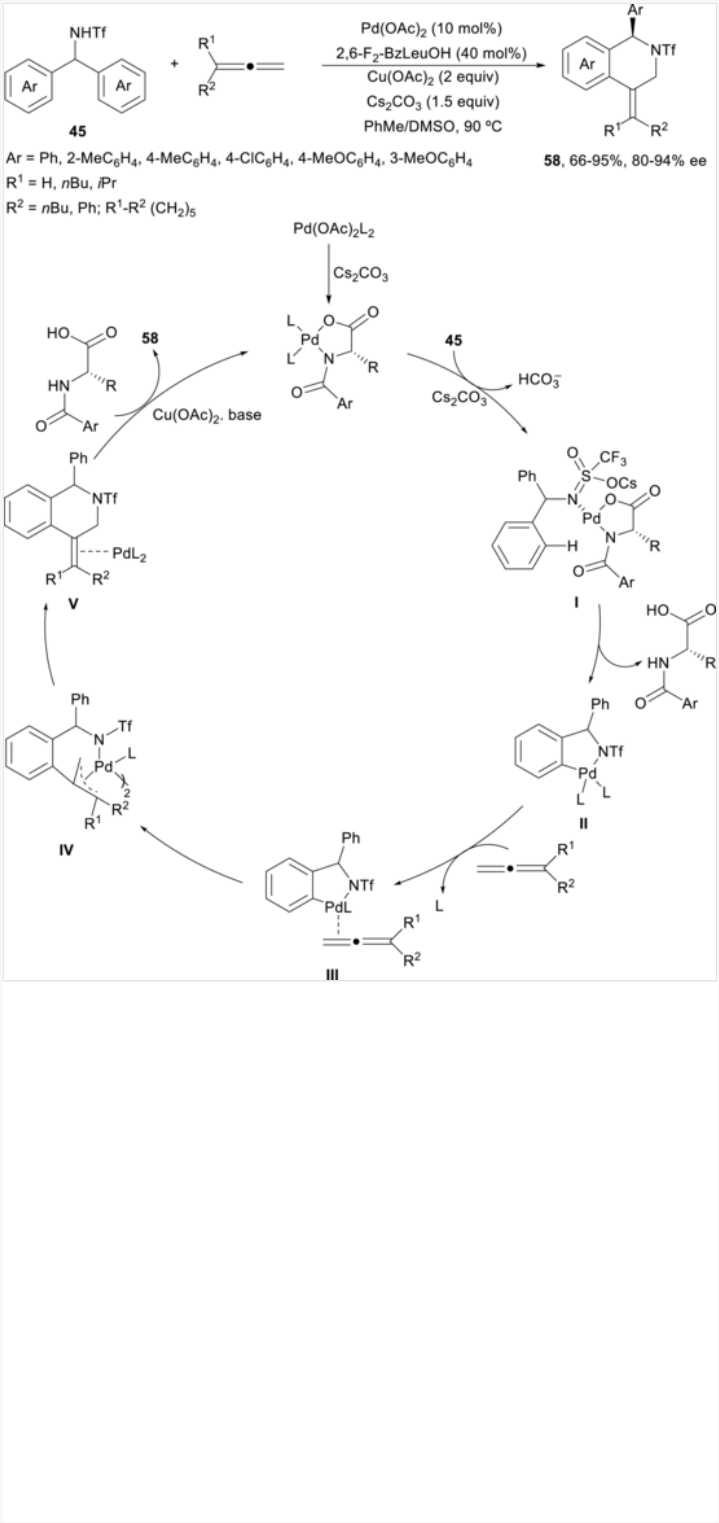


Ir-Catalyzed desymmetrization of diarylmethylamides **52** and **56** by an enantioselective remote C–H borylation.

Formal cycloaddition of allenes with benzyl and allyltriflamides has been applied to the desymmetrization of diarylmethyltriflamides **45** [53]. Under Pd/Cu catalysis and 2,6-F_2-BzLeuOH as a chiral ligand this cycloaddition takes place by C–H activation to provide isoquinolines **58** with high enantioselectivity (Scheme 16). In the proposed catalytic cycle after coordination of **45** to the catalyst intermediate like **I** can be formed, which underwent C–H activation to give intermediate **II**. After coordination of **II** with the allene to form **III**, a migratory insertion afforded a π-allylpalladacycle **IV**, which experimented reductive elimination to generate **V**. Final oxidation of Pd(0) to the active Pd(II) catalyst furnished product **58**.

alt-text: Scheme 16

Scheme 16



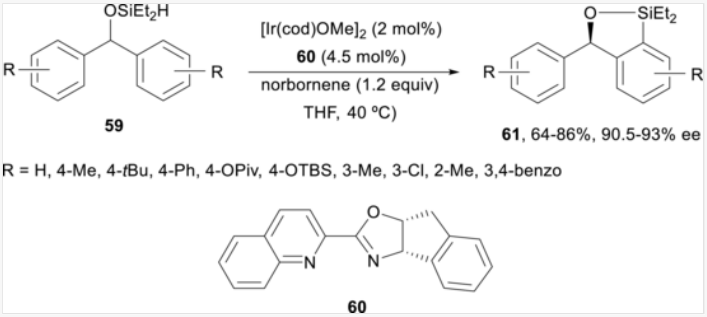
Pd-Catalyzed desymmetrization of diarylmethyltriflamides **45** by an enantioselective formal [4 + 2] annulation with allenes.

2.3 Other diarylmethane compounds

Shi, Hartwig and co-workers [54] have described an Ir-catalyzed desymmetrization of *O*-silylated diarylmethanols **59** by silylation of aromatic C–H bonds. They used a chiral pyridinyloxazolidine ligand **60** for the enantioselective intramolecular silylation of compounds **59** to afford cyclic silanes **61** in good yields and enantioselectivities (Scheme 17). The same selective transformation has been carried out under kinetic resolution conditions.

alt-text: Scheme 17

Scheme 17

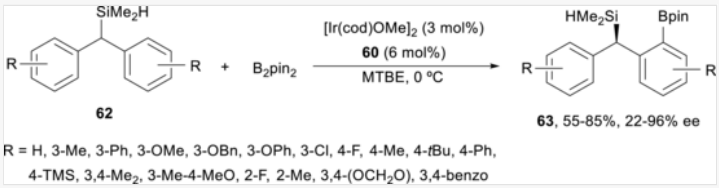


Ir-Catalyzed desymmetrization of *O*-silylated diarylmethanols **59** by an enantioselective intramolecular C–H silylation.

The same group reported [55] the desymmetrization of diarylmethylsilanes **62** by enantioselective Ir-catalyzed C–H borylation (Scheme 18). In this case, ligand **60** was also used to provide products **63** in moderate to good yields and enantioselectivities. These products were further transformed into an alcohol-phenol by oxidation of both C–Si and C–B bonds. Other processes such as reaction with $CuCl_2$ or $CuBr_2$, led to the conversion of the C–B bond to C–Cl or C–Br, respectively. By means of a Suzuki reaction arylation of the C–B bond has been also performed.

alt-text: Scheme 18

Scheme 18

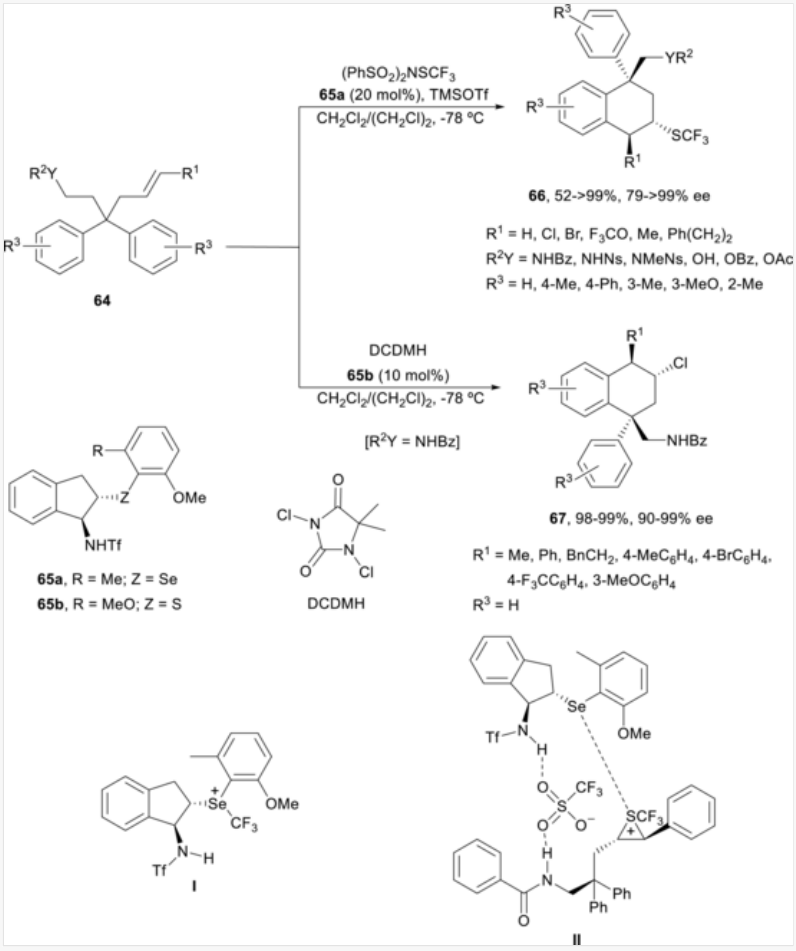


Ir-Catalyzed desymmetrization of diarylmethylsilanes **62** by an enantioselective C–H borylation.

For the desymmetrization of *gem*-diaryl-tethered alkenes **64** it has been used an enantioselective trifluoromethylthiolation catalyzed by a bifunctional selenide organocatalyst **65a** (Scheme 19) [56]. As starting materials olefinic benzamides, alcohol derivatives were mainly studied to give the corresponding trifluoromethylthiolated tetrahydronaphthalenes **66** bearing an all-carbon quaternary stereocenters. The reaction was performed in gram-scale and the catalyst recycled during at least five times maintaining the yield and enantioselectivity. Products **66** were further transformed into other sulfur derivatives by oxidation. On the basis of experimental and DFT calculations it was proposed the formation of intermediate **I** between the catalyst and the CF_3S reagent in the presence of the Lewis acid TMSOTf. This intermediate **I** reacts with the substrate **64a** to give intermediate **II** and then the final product **66a**. This process has been also applied to a couple of tethered alkynes to furnish the corresponding dihydronaphthalenes in 68–73% yield and 87–95% ee. The same substrates **64** have been submitted to desymmetrization by chlorination with dichlorodimethylhydantoin (DCDMH) as chlorine source [57]. In this case, a similar chiral sulfide **65b** was used in the presence of bistriflamide in CH_2Cl_2 at −78 °C to provide tetralines **67** in high yields and enantioselectivities (Scheme 19).

alt-text: Scheme 19

Scheme 19



Organocatalyzed desymmetrization of diaryl-tethered alkenes **64** by an enantioselective trifluoromethylthiolation and chlorination.

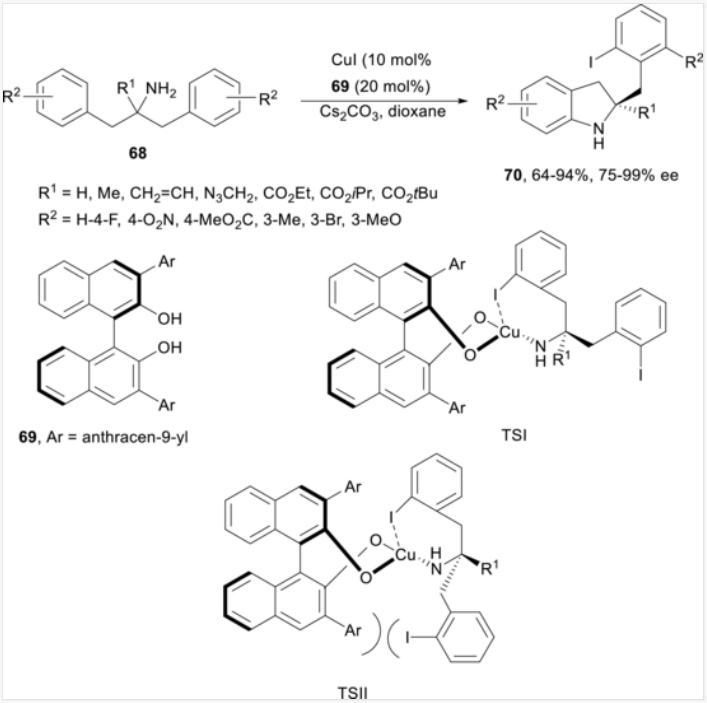
2.4 Dibenzylalkane derivatives

Dibenzylmethylamines have been desymmetrized by a Cu-catalyzed intramolecular Ullman reaction and by C–H carbonylation and acylation reactions.

Intramolecular copper-catalyzed asymmetric *N*-arylation of dibenzylmethylamines has been reported by Cai and co-workers [58]. This Ullmann coupling reaction was carried out using compounds **68** and the BINOL derivative **69** under mild reaction conditions to afford indolines **70** in good yields and enantioselectivities (Scheme 20). Based on experimental observations, **TSI** suffered less steric interactions between the aryl group of the ligand and the aryl group of compound **68** as it happens in **TSII**. This strategy was also applied to homologous compounds to provide the corresponding six-membered ring of 1,2,3,4-tetrahydroquinolines.

alt-text: Scheme 20

Scheme 20



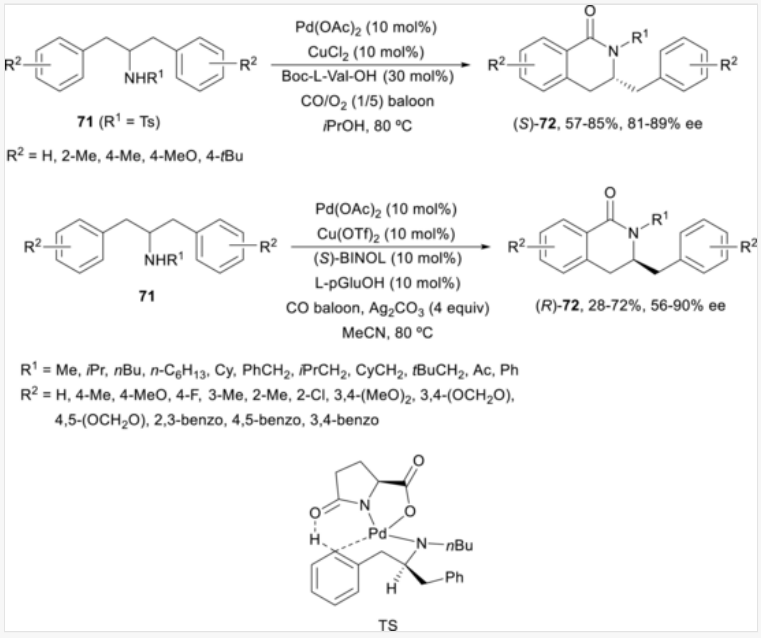
Cu-Catalyzed desymmetrization of dibenzylmethylamines **68** by an enantioselective Ullmann reaction.

The asymmetric carbonylation of *N*-sulfonyl diarylmethylamines [49] (Scheme 12) has been also applied to dibenzylmethylamines **71** to give *N*-tosyl isoquinolines (*S*)-**72** in moderate to good yields and lower enantioselectivities that to five membered compounds **70** (Scheme 21). These results indicated that the bigger cyclic transient state in the C–H activation step impeded the stereocontrol. This type of C–H aminocarbonylation was reported simultaneously with *N*-alkyl substituted dibenzylmethylamines **71** by Lan, Xia and co-workers [60]. They employed L-pyroglutamic acid (L-pGluOH) as a chiral ligand, (*S*)-BINOL as additive and Ag_2CO_3 as oxidant in acetonitrile with a CO balloon at 80 °C (Scheme 21). The resulting products (*R*)-**72** were isolated in low to moderate yields and enantioselectivities. In this case **TS** was proposed as the most favorable one according to DFT calculations.

Images are optimised for fast web viewing. Click on the image to view the original version.

alt-text: Scheme 21

Scheme 21

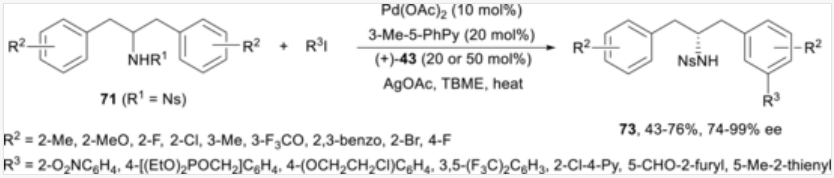


Pd/Cu-Catalyzed desymmetrization of *N*-tosyl dibenzylmethylamines **71** by enantioselective C–H carbonylations.

Yu and co-workers [47] applied the intermolecular C–C arylation of diarylmethylamines **41** (Scheme 11) to homologous *N*-nosyl dibenzylmethylamines **71** (R^1 = Ns). This enantioselective *meta*-C–H arylation was carried out with (+)-NBE-CO_2Me (**43**) as a chiral ligand in the presence of 3-methyl-5-phenylpyridine affording products **73** in moderate to good yields and good to high enantioselectivities (Scheme 22). Not only aryl iodides, but also 2-bromobenzoate and iodoacetate gave products **73** in 99 and 84% ee, respectively.

alt-text: Scheme 22

Scheme 22

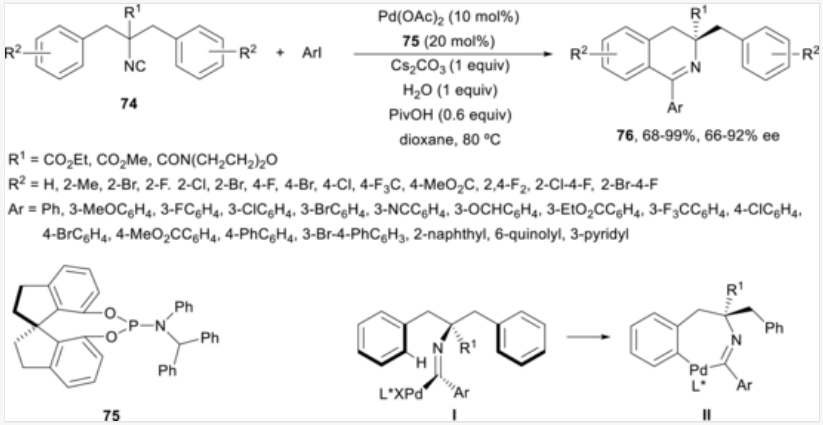


Pd-Catalyzed desymmetrization of *N*-tosyl dibenzylmethylamines **71** by an intramolecular *meta*-C–H arylation.

Dibenzylmethyl isocyanides **74** have been submitted to desymmetrization by a Pd-catalyzed enantioselective C–H imidoylation (Scheme 23) [61]. The reaction took place using a chiral SPINOL-derived phosphoramidite **75** as ligand by isocyanide insertion into the aryl-Pd to give intermediate **I** followed by C–H activation to give palladacycle **II**. Final reductive elimination furnished 3,4-dihydroisoquinolines **76** in high yields and good enantioselectivities.

alt-text: Scheme 23

Scheme 23



Pd-Catalyzed desymmetrization of dibenzylmethyl isocyanides **74** by an enantioselective C–H imidoylation.

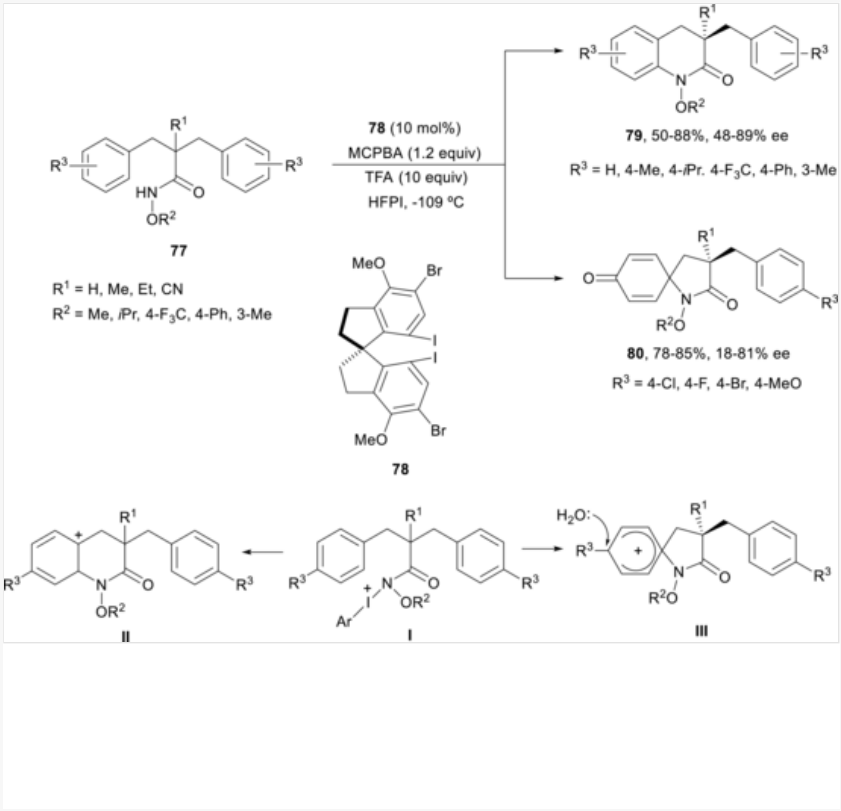
A chiral hipervalent iodine generated by oxidation of diiodospirobiindane **78** has been employed as catalyst for the enantioselective oxidative C–N bond formation of dibenzyl hydroxamates **77** by Cai and co-workers (Scheme 24) [62] Using MCPBA as oxidant, TFA as additive and hexafluoroisopropanol (HFIP) as solvent at −10 °C the corresponding lactamization gave tetrahydroquinolines **79** in good yields and stereoselectivities. However, when compounds **77** beard a halide or RO groups at the *para*-positions an oxidative spirocyclization with concomitant dearomatization occurred to provide spirolactams **80** in good yields and modest enantioselectivities. In the proposed mechanism, a nitrenium ion **I** would be intermediate for the two intramolecular attacks to the aryl unit. Intermediate **II** could furnish lactams *via*

simple elimination, whereas intermediate **III**, after water attack to the *para*-position, gave spirolactams **80** or suffered N-migration to form intermediate **I**.

Images are optimised for fast web viewing. Click on the image to view the original version.

alt-text: Scheme 24

Scheme 24



Aryliodine-catalyzed desymmetrization of dibenzyl hydroxamates **77** by an enantioselective intramolecular C–H bond formation.

3 Desymmetrization of dienes, diynes and other unsaturated compounds

Intramolecular metal-catalyzed cyclizations either by ring-closing methatesis, hydroacyclation and cycloisomerization have been mainly employed for the desymmetrization of dienes and diynes. Other general strategies involve halocyclization processes and intramolecular organocatalyzed hydroamination reactions.

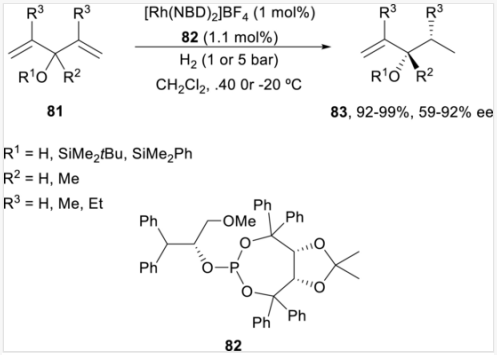
3.1 Dienes

In this Section, recent desymmetrization of acyclic and cyclic dienes under transition metal catalysis [13] or using asymmetric organocatalysis [12] are considered. Acyclic 1,4-dienes **84** have been desymmetrized by Rh-catalyzed hydrogenation [6] using a TADDOL-derived phosphite **82** as a chiral ligand (Scheme 25) [63]. This catalyst is able to differentiate the two enantiotopic vinyl groups, working at low temperature and under 1 or 5 bar H_2 pressure, to give the corresponding allylic alcohols **83** with full conversion and moderate to good enantioselectivity.

Images are optimised for fast web viewing. Click on the image to view the original version.

alt-text: Scheme 25

Scheme 25



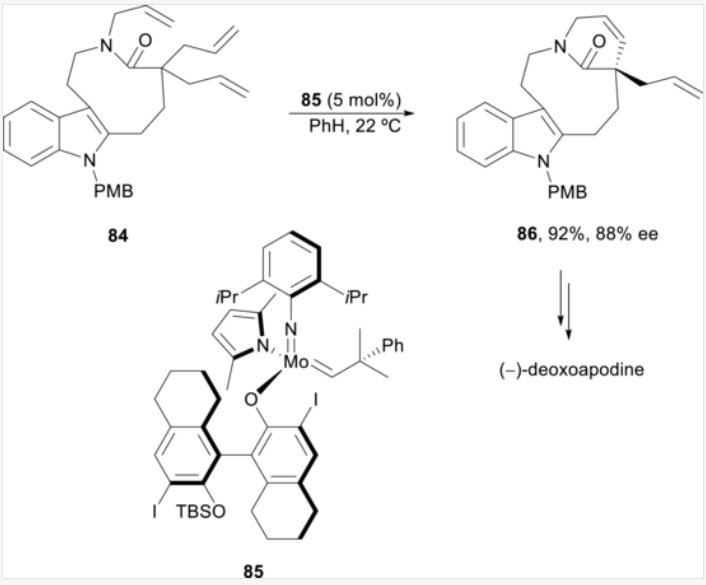
Rh-Catalyzed desymmetrization of 1,4-dienes **81** by an enantioselective hydrogenation.

Movassaghi and co-workers [64] performed the enantioselective total synthesis of the aspidosperma alkaloid (−)-deoxoapodine using as the key step the desymmetrization of lactam **84** [65] bearing a 1,4-diene unit. Ring-closing metathesis (RCM) reaction of **84** with the Mo monoaryloxide pyrrole **85** delivered (+)-lactam **86** in 92% yield and 88% ee (Scheme 26).

Images are optimised for fast web viewing. Click on the image to view the original version.

alt-text: Scheme 26

Scheme 26

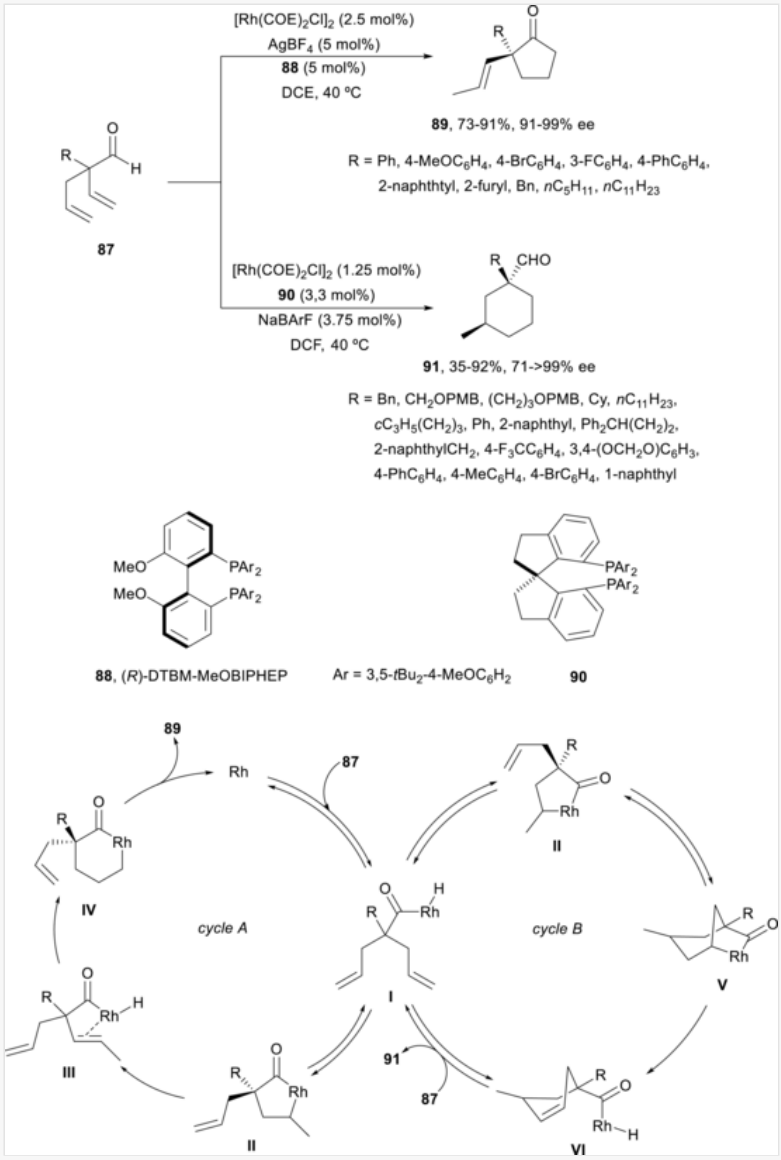


Mo-Catalyzed desymmetrization of 1,4-diene **84** by an enantioselective RCM.

1,6-Dienes **87** bearing a formyl group have been submitted to a Rh-catalyzed desymmetrization using chiral phosphines [66,67]. In the case of using ligand **88** an isomerization followed by hydroacylation provided cyclopentanones **89** [66], whereas ligand **90** gave an enantioselective cycloisomerization affording cyclohexenecarbaldehydes **91** [67] (Scheme 27). In the mechanism proposed (cycle A) for the formation of cyclopentenones **89** [66] once the acyl-rhodium hydride **I** was formed, insertion of the olefin into the Rh(III)–H bond afforded metalacycle **II**. After endocyclic β-hydride elimination, intermediate **III** is formed, which by insertion of the olefin provided the six-membered rhodacycle **IV**. Final reductive elimination afforded products **89**. The bite angle of the rigid ligand **90** (96.2°) is critical for promoting carbocyclization to products **91** [66]. In the catalytic cycle B, rhodacycle **II** experiments carbometalation into the olefin to give intermediate **V**, which after β-hydride elimination furnished the acylRh(III)hydride **VI**. Final reductive elimination gave products **91**.

alt-text: Scheme 27

Scheme 27

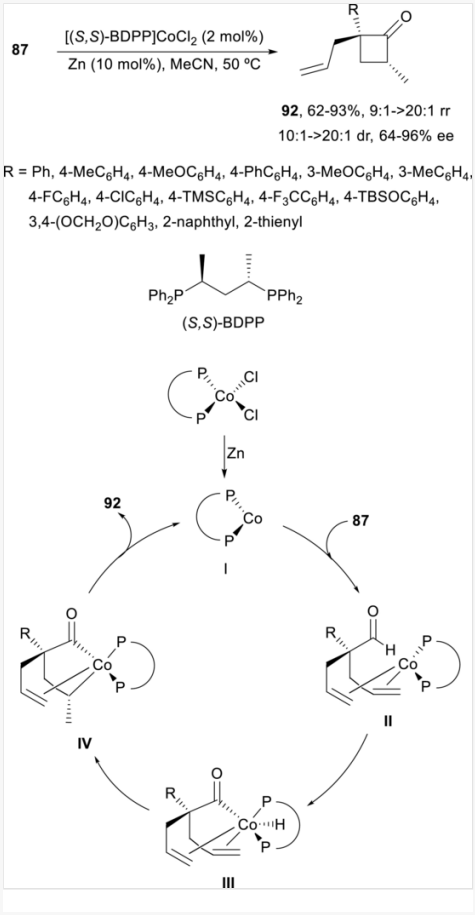


Rh-Catalyzed desymmetrization of α,α-bisallylaldehydes **87** under ligand control by an enantioselective isomerization-acylation.

Not only Rh but also Co activate aldehyde C−H bonds through oxidative addition giving in this case cyclobutanones. Dong and co-workers [68] reported the Co-hydroarylation of α,α-bisallylaldehydes **87** using [(*S,S*)-BDPP]$CoCl_2$ as catalyst in the presence of Zn as reductant (Scheme 28). The corresponding cyclobutanones **92** were obtained with high regio-, diastereo- and enantioselectivity. It was postulated that the reductant transforms Co(I) complex into a Co(0) **I**. This catalyst **I** binds to the substrate to form **II** and then aldehyde C–H oxidative addition gave intermediate **III**. After olefin insertion a five membered metalacycle **IV** is formed, which by reductive elimination provided products **92**.

alt-text: Scheme 28

Scheme 28

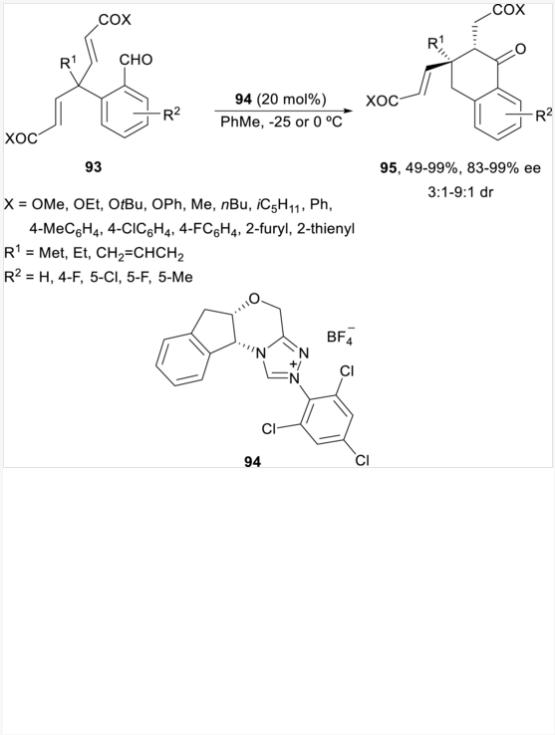


Co-Catalyzed desymmetrization of α,α-bisallylaldehydes **87** by an enantioselective hydroacylation.

Organocatalyzed desymmetrizations have been applied to 1,4- and 1,6-dienes. Functionalized 1,4-dienes were desymmetrized by Yang, Fang and co-workers [69] *via* an enantioselective Stetter reaction. Using a chiral N-heterocyclic carbene (NHC) precursor **94**, ester and ketone derivatives **93** underwent annulation to provide diastereoselectively tetralones **95** with two consecutive stereocenters in good yields and high enantioselectivities (Scheme 29). This transformation has been applied to other different substrates giving the corresponding products with lower enantioselectivities.

alt-text: Scheme 29

Scheme 29



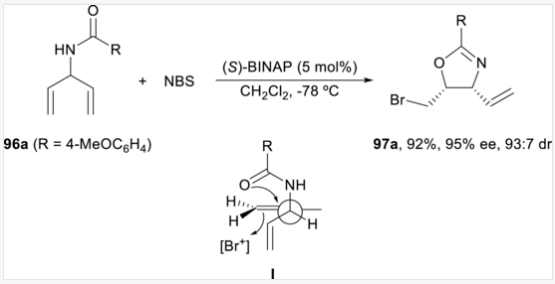
NHC-Catalyzed desymmetrization of functionalized 1,4-dienes **93** by an enantioselective Stetter reaction.

Organocatalyzed enantioselective haloetherifications have been applied the desymmetrization of dienes [12,70]. Hamashima and co-workers [71,73] have studied the enantioselective bromocyclization of 1,4-dienes bearing an amide at the allylic position using BINAP monoxide or BINAP as chiral organocatalysts. This desymmetrization strategy has been applied as the key step toward the enantioselective synthesis of the HIV-protease inhibitor, nelfinavir [73]. Starting from the 1,4-diene **96a** the corresponding bromocyclization with NBS and (*S*)-BINAP as catalyst gave the oxazoline **97a** in 92% yield and 95% ee for the *cis*-isomer with a 93:7 *cis/trans* diastereomeric ratio (Scheme 30). This product was further transformed into nelfinavir. The stereochemical model **I** for this type of bromocyclization is represented in Scheme 30.

Images are optimised for fast web viewing. Click on the image to view the original version.

alt-text: Scheme 30

Scheme 30

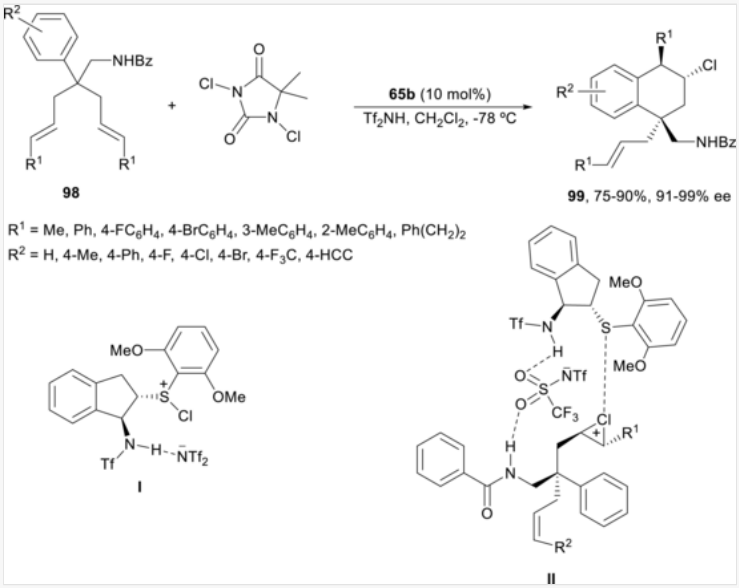


BINAP-Catalyzed desymmetrization of 1,4-diene **96a** by an enantioselective bromocyclization.

1,6-Dienes such as bis-alkenoic acids have been desymmetrizated by bromolactonization by Nennecke and co-workers [74]. Recently Zhao and co-workers [57] reported a chiral sulfide **65b** catalyzed desymmetrization of diallyl *N*-benzoyl methylamines **98** by enantioselective chlorination (Scheme 31). Using dichlorodimethylhydantoin (DCDMH) as chlorine source and **65b** as catalyst compounds **98** afforded tetralins **99** bearing three stereocenters in high yields enantio- and diastereoselectivities. According to experimental results intermediate **I** was initially formed by the reaction of catalyst and DCDMH, which interacts with the 1,6-diene **98** to give intermediate **II** with an acid-derived anion bridge through a hydrogen bond.

alt-text: Scheme 31

Scheme 31

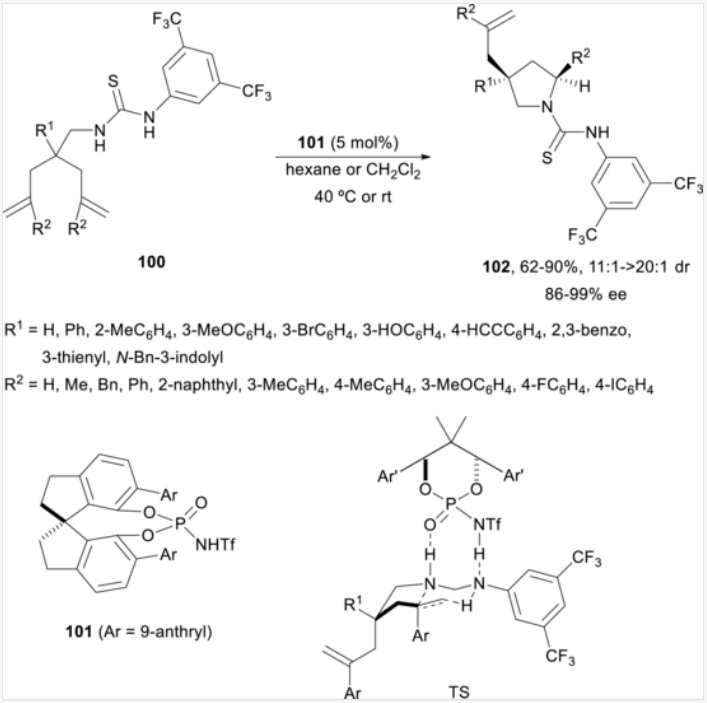


Chiral sulfide **65b** catalyzed desymmetrization of 1,6-dienic amides **98** by an enantioselective chlorination.

Electrophile-induced desymmetrization of 1,6-dienes **100** has been performed *via* intramolecular hydroamination by chiral Brønsted acid catalysis [75]. After evaluation of different protecting groups in the amino moiety, thiourea gave the best results. Concerning the organocatalyst, *N*-triflyl phosphoramidate **101** provided better enantiocontrol giving enantioenriched pyrrolidines **102** in good yields and high diastereo- and enantioselectivities (Scheme 32). On the basis of experimental studies, the authors proposed that the hydroamination proceeds through a concerted mechanism. The chiral catalyst **101** activates the substrate through a hydrogen bonding with the NH and the basic oxygen deprotonates the other NH group. In this **TS** the *Si*-face of the allylic chain was favored due to the steric hindrance between the Ar group on the alkene and the bulky 3,3′-substituents on the catalyst.

alt-text: Scheme 32

Scheme 32

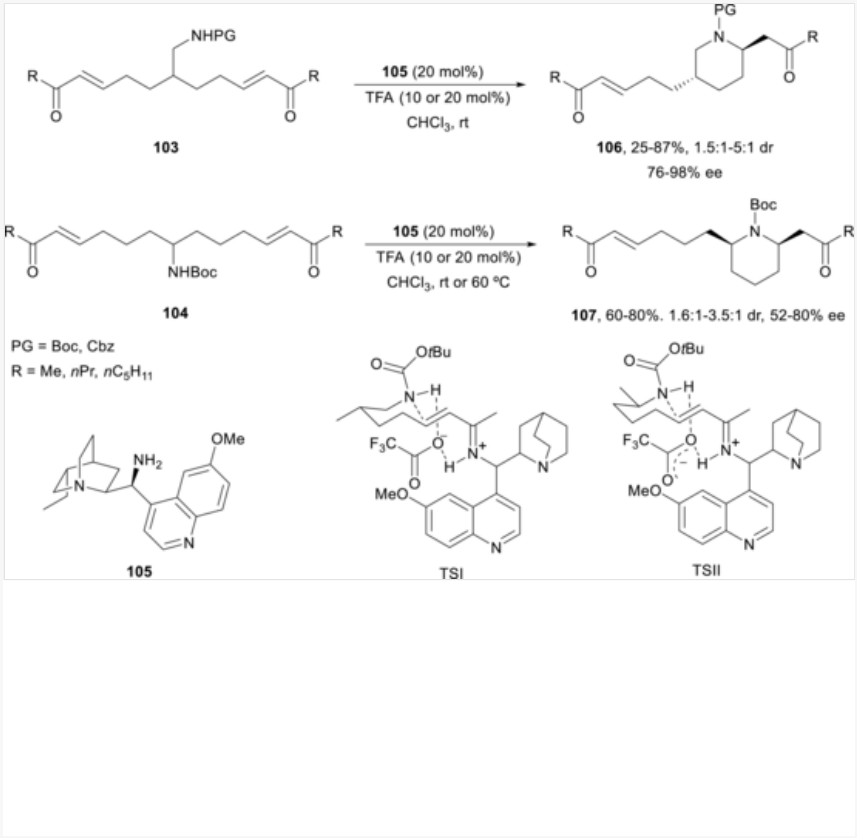


Brønsted acid-catalyzed desymmetrization of 1,6-dienes **100** by an intramolecular hydroamination.

Del Pozo and co-workers [76] applied an organocatalytic enantioselective intramolecular aza-Michael reaction to the desymmetrization of bis-enones **103** and **104** (Scheme 33). By using of 9-amino-9-deoxy-*epi*-hydroquinone **105** as catalyst and trifluoroacetic acid as co-catalyst enantiomerically enriched *trans*-2,5- and *cis*-2,6-disubstituted piperidines **106** and **107** were mainly obtained in good yields, moderate diastereoselectivity and good enantioselectivity for the major diastereomers. From experimental and theoretical studies simplified **TSI** has been proposed for the formation of the major *trans*-2,5-isomer **106** and **TSII** for the *cis*-2,6-isomer **107**.

alt-text: Scheme 33

Scheme 33

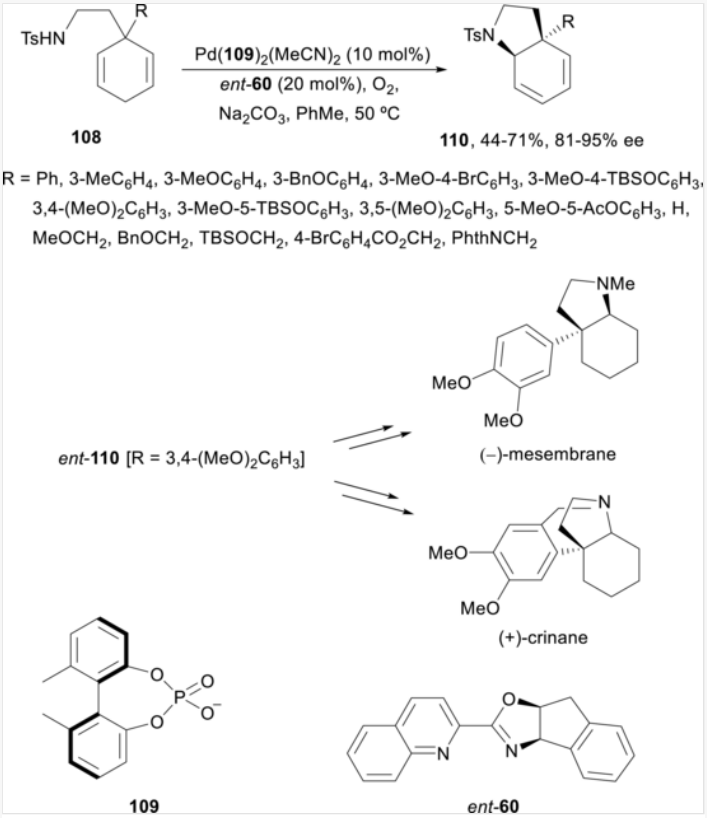


Amine-catalyzed desymmetrization of bis-enones **103** and **104** by an enantioselective intramolecular aza-Michael reaction.

Prochiral cyclic dienes desymmetrization has been carried out mainly by Pd-catalyzed intramolecular Heck reactions, cross-coupling reactions and carbonylation reactions [13]. Other intramolecular metal-catalyzed reactions by Zr and Cu have been also reported [77]. Recent advances in this field involved an aza-Wacker reaction which was applied to the total synthesis of (−)-mesembrane and (+)-crinane by Zhu and co-workers [78]. 3,3-Disubstituted 1,4-cyclohexadienes **108** underwent enantioselective desymmetrization using Pd(**109**)$_2$(MeCN)$_2$ as catalyst and the chiral ligand *ent*-**60** in the presence of oxygen (Scheme 34). Enantioenriched *cis*-3a-substituted tetrahydroindoles **110** were obtained in good yields and excellent enantioselectivities. A cooperative effect between the chiral pyrox ligand *ent*-**60** and the phosphoric acid anion of the Pd complex **109** increased both the yield and the enantiocontrol.

alt-text: Scheme 34

Scheme 34

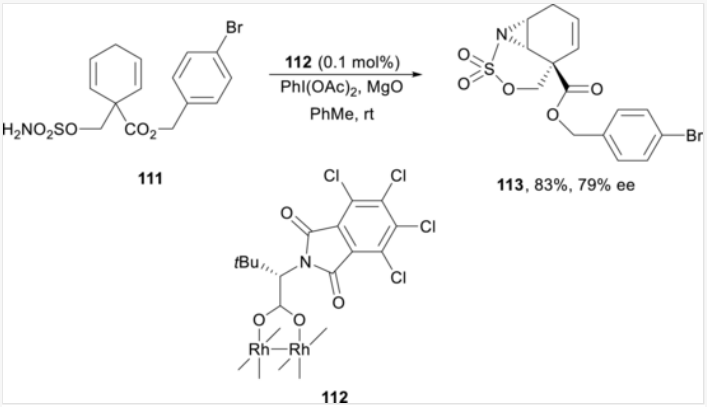


Pd-Catalyzed desymmetrization of 1,4-cyclohexadienes **108** by an enantioselective aza-Wacker cyclization.

Kan and co-workers [79] described the desymmetrization of cyclohexadiene **111** [80] by Rh-catalyzed aziridination to give compound **113** (Scheme 35). Sulfonamide **111** was treated with Rh_2(*S*-TCPTTL)$_4$ (**112**) in the presence of PhI(OAc)$_2$ and MgO in toluene at room temperature giving **113** in 83% yield and 79% ee. This aziridine **113** was further transformed into the cyclopentane core of the aminocyclopentitol antibiotic pactamycin.

alt-text: Scheme 35

Scheme 35

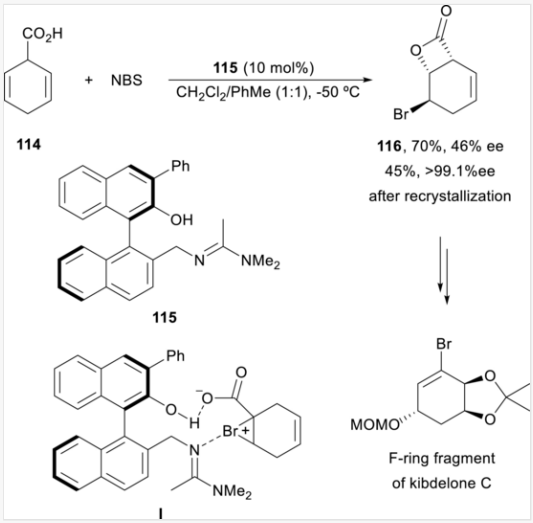


Rh-Catalyzed desymmetrization of cyclohexadiene **111** by an enantioselective aziridination.

Desymmetrization of dienes by asymmetric halocyclization [70] has been applied also to cyclohexadienes. Klosowski and Martin [81] reported the asymmetric bromolactonization of 1,4-dihydrobenzoic acid (**114**) using BINOL-amidine catalyst **115** [82] (Scheme 36). The resulting lactone **116** was obtained in 70% yield and moderate enantioselectivity, which after a single recrystallization provided enantiopure **116** in 45% yield on a multigram scale. The authors propose that the basic amidine group in **115** stabilizes the bromonium intermediate, whereas the acidic phenol group associates the carboxylic acid as it is shown in model **I**. Compound **116** was transformed into the F-ring fragment of the natural product kibdelone C.

alt-text: Scheme 36

Scheme 36

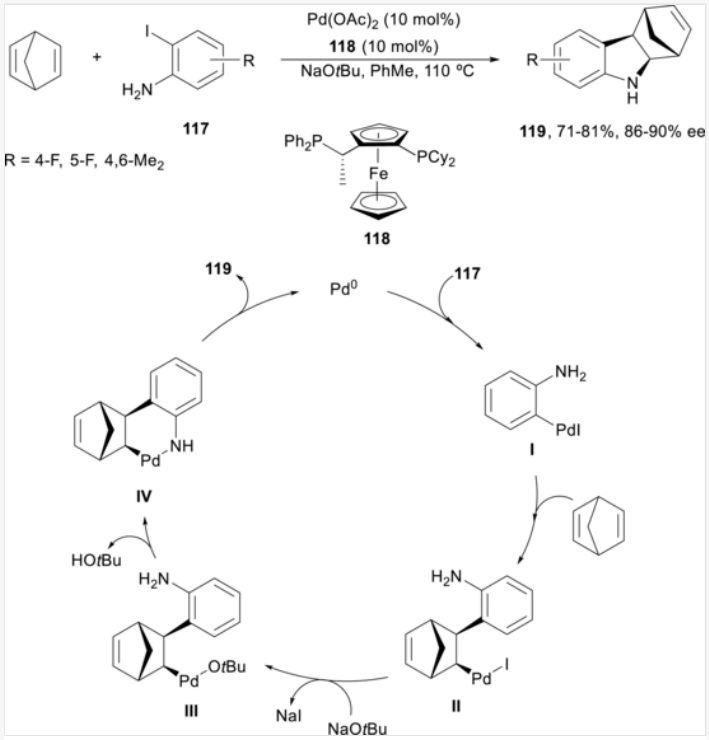


BINOL-amidine-catalyzed desymmetrization of cyclohexadienecarboxylic acid **114** by an enantioselective bromolactonization.

Desymmetrization of norbornadiene has been carried out by Gansäuer and co-workers [83] *via* a Pd-catalyzed carboamination with iodides **117** using a Josiphos ligand **118** giving products **119** with the highest enantioselectivities (Scheme 37). In the proposed catalytic cycle the intermolecular carbopalladation of norbornadiene by intermediate **I** gave intermediates **II** and **III**. The formation of palladacycle **IV** by deprotonation of intermediate **III** gave the indoline **119** after reductive elimination.

alt-text: Scheme 37

Scheme 37



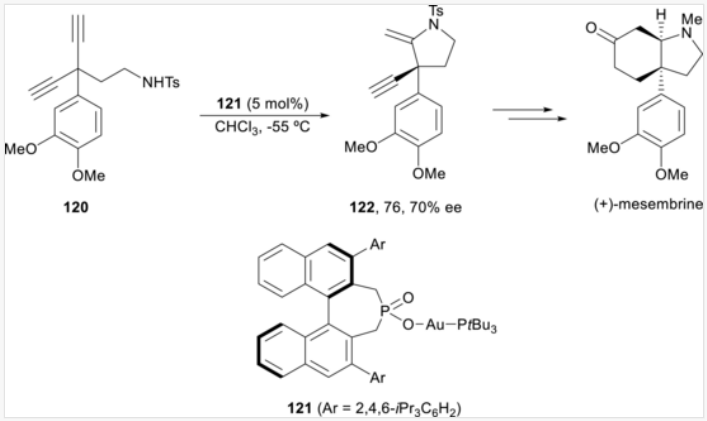
Pd-Catalyzed desymmetrization of norbornadiene by an enantioselective carboamination.

3.2 Diynes

1,4-Diynes have been cycloisomerized using asymmetric gold catalysis and applied to the total synthesis of the alkaloid (+)-mesembrine by Czekelius and co-workers [84,85]. Starting from 1,4-diynamide **120**, the corresponding methylene pyrrolidines **122** was obtained in 76% ee using the BINOL-derived gold(I) catalyst **121** (Scheme 38) previously used by the same group [86] for the desymmetrization of 1,4-diynols and 1,4-diynamides in 67–99% yields and 74–92% ee.

alt-text: Scheme 38

Scheme 38



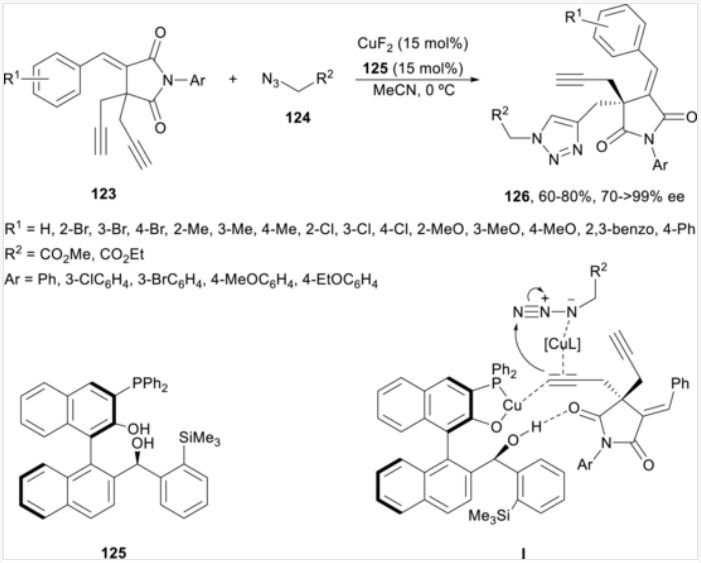
Au(I)-Catalyzed desymmetrization of 1,4-diynamide **120** by an enantioselective cycloisomerization.

An asymmetric Cu(I).catalyzed azide-alkyne cycloaddition (ACAAC) has been used in the desymmetrization of 1,6-diynes [87–89]. Zhou and co-workers [87] performed the ACAAC of oxindole-based 1,6-heptadiynes using a Pybox ligand. Xu and c-workers [88] developed the desymmetrization of succinimides-derived bis(alkynes) **123** by reaction with azide **124** using TaoPhos **125** and CuF_2 in good yields and enantioselectivities (Scheme 39). This process has been carried out also with benzylazides **124** (R^2 = Ar) with 20 mol% catalyst loading and in the presence of Et_3N to give products **126** in 60–81% yield and up to 97% ee. Experimental studies and ESI-MS analysis suggested the participation of a binuclear copper catalyst in intermediate **I**.

Images are optimised for fast web viewing. Click on the image to view the original version.

alt-text: Scheme 39

Scheme 39

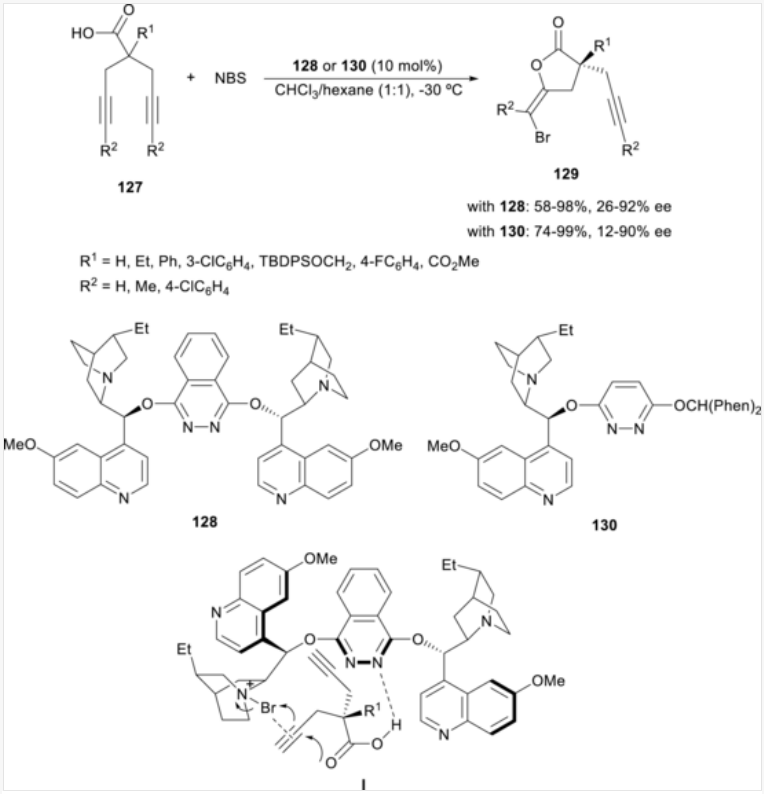


Cu-Catalyzed desymmetrization of succinimide-derived 1,6-heptadiynes **123** by azide-alkyne click cycloaddition.

Desymmetrization by halocyclization reactions [70] has been applied to 1,6-diynes by Hennecke's group [90–92]. Bromolactonization of diynoic acids **127** with NBS and the dimeric *Cinchona* alkaloid-based catalyst $(DHQD)_2PHAL$ **128** (10 mol%) gave bromoenol lactones **129** in good yields and enantioselectivities (Scheme 40) [90]. Further studies of the group demonstrated that the monomeric dihydroquinidine-based catalyst **130** can also be used giving similar results [91]. Intermediate **I** has been proposed to explain the stereochemical results with catalyst **128**. An enantioselective iodolactonization of the same diynoic acids using NIS and organocatalyst **128** gave the corresponding iodoenol lactones in 71–99% yields and 42–82% ee.

alt-text: Scheme 40

Scheme 40



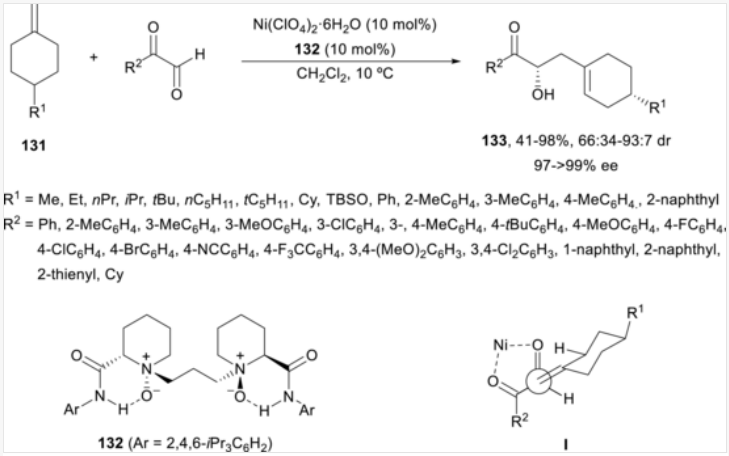
Organocatalyzed desymmetrization of 1,6-diynes **127** by an enantioselective bromolactonization.

3.3 Other unsaturated compounds

1-Substituted 4-methylenecyclohexanes **131** have been desymmetrized by an enantioselective carbonyl-ene reaction [93]. The reaction of compounds **131** with glyoxal derivatives took place under Ni-catalysis using a *N,N′*-dioxide **132** as a chiral ligand to provide cyclohexenes **133** bearing two remote 1,6-related stereocenters (Scheme 41). In the proposed simplified transition state **I** the glyoxal derivative is activated by coordination with the Ni(II) by the dicarbonyl groups. The *Re* face of glyoxal is blocked by the 2,4,6-triisopropylphenyl group of the ligand leading to the predominant *Si* face addition.

alt-text: Scheme 41

Scheme 41

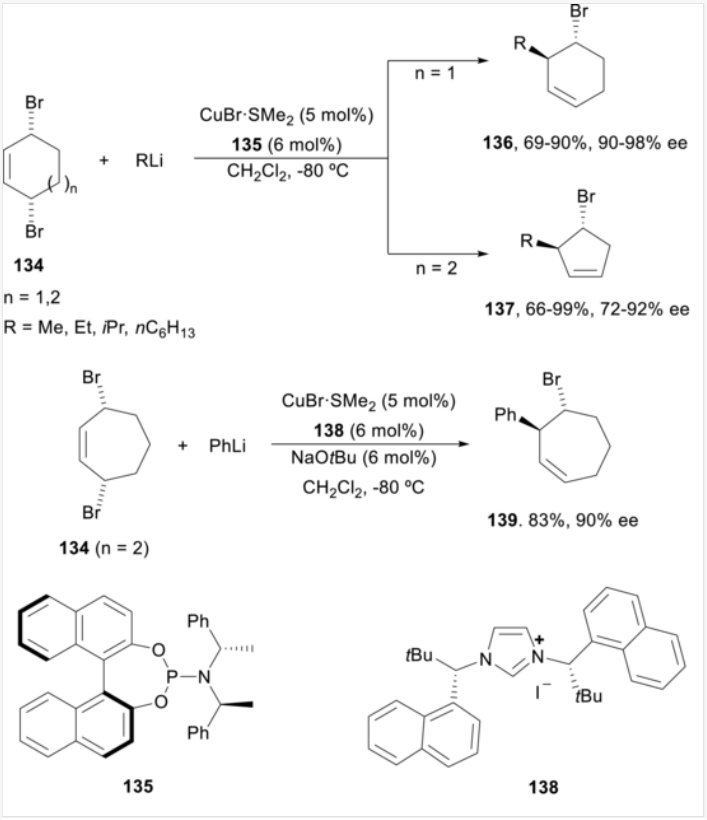


Ni-Catalyzed desymmetrization of 4-methylenecyclohexanes **131** by an enantioselective carbonyl-ene reaction.

The most commonly employed procedure for desymmetrization of *meso*-cycloalk-2-ene-1,4-diol derivatives is the asymmetric Pd or Ru-catalyzed allylic substitution [94]. Recently, desymmetrization of *meso*-1,4-dibromocyclohexenes and cycloheptenes has been performed by Feringa and co-workers [95] using Cu(I)-catalyzed allylic substitution. In this case 1,4-dibromocycloalkenes **134** were allowed to react with organolithium reagents using CuBr and the chiral phosphoramidite **135** as ligand (Scheme 42). Cyclohexene derivatives **136** were obtained whereas cycloheptenes underwent an unusual ring contraction giving cyclopentenes **137**. However, using the NHC precursor **138** as ligand, *meso*-dibromocycloheptene reacted with PhLi to provide product **139**. The obtained 6 and 7-membered products **136** and **138** were further derivatized to give amino alcohols.

alt-text: Scheme 42

Scheme 42



Cu-Catalyzed desymmetrization of *meso*-dibromocycloalkenes **134** by an enantioselective allylic substitution with organolithiums.

4 Desymmetrization of diols and polyols

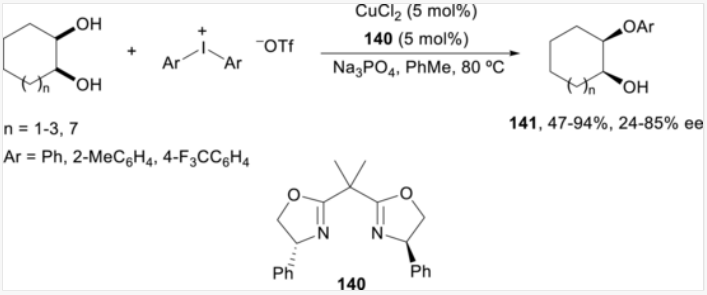
In this Section desymmetrization of 1,2- and 1,3-diols as well as other diols and polyols will be considered using mainly monoprotection strategies.

4.1 1,2-Diols

Enantioselective protection of acyclic and cyclic *meso*-1,2-diols included mainly organocatalytic and enzymatic methods [4,5,9,12,16,21,24,25] by metal-catalyzed arylation, esterification, silylation and oxidation reactions. Recently, metal-catalyzed etherification reactions of cyclic *meso*-1,2-diols and 2,3-butanediol have been achieved by Cu-catalyzed asymmetric monoarylation with diaryliodonium salts [96]. Bis(oxazoline) ligand **140** gave the corresponding β-aryloxy alcohols **141** in moderate to very good yields and moderate enantioselectivities (Scheme 43).

alt-text: Scheme 43

Scheme 43

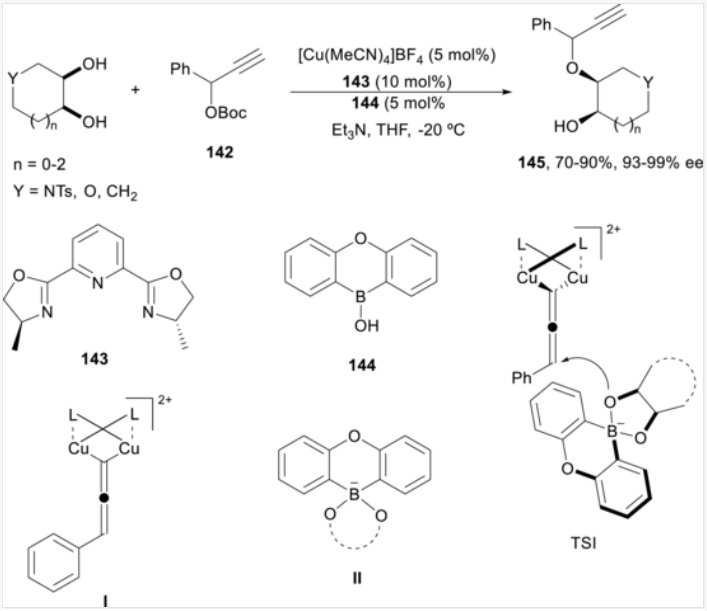


Cu-Catalyzed desymmetrization of *meso*-1,2-diols by an enantioselective monoarylation with diaryliodonium salts.

Monopropargylation of cyclic *meso*-1,2-diols and 3,4-hexanediol with Boc-protected 1-phenylpropargyl alcohol **142** has been carried out using an enantioselective Cu(I)-catalyzed etherification by Miu and co-workers [97]. This reaction was performed using catalytic amounts of borinic acid **144** and the bis(oxazolidine) chiral ligand **143** to provide products **145** in very good yields and enantioselectivities (Scheme 44). This Cu/B dual catalytic desymmetrization took place by formation of a dicopper-allenylidene species **I**, which underwent nucleophilic attack at the γ-C atom from the *Re* face by the boron 'ate' complex **II**. According to DFT calculations **TS** has been proposed to rationalize the observed selectivity.

alt-text: Scheme 44

Scheme 44

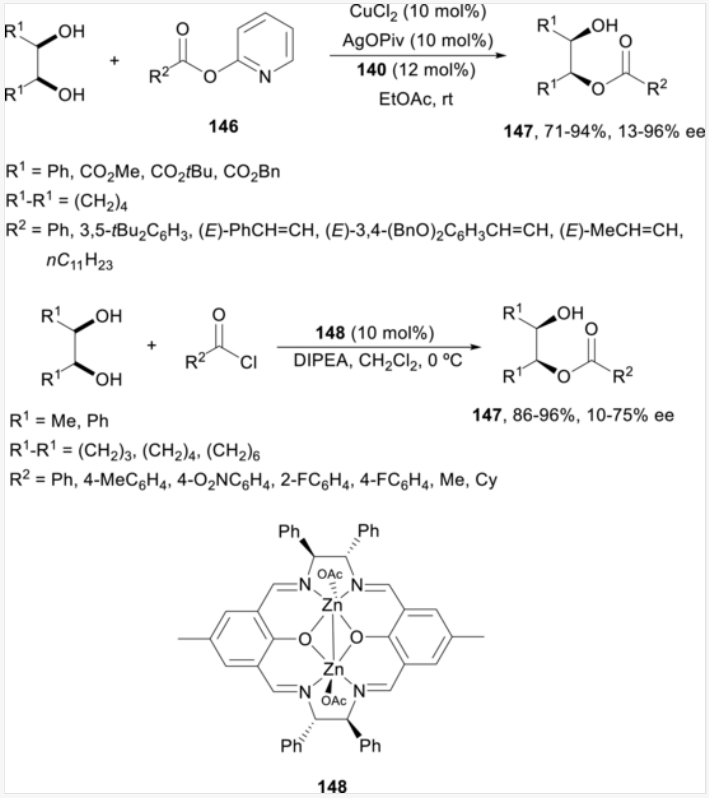


Cu/B-Catalyzed desymmetrization of *meso*-1,2-diols by an enantioselective propargylation with **142**.

Sugiura and co-workers [98] reported the monoacylation of *meso*-1,2-diols including dialkyl *meso*-tartrates using 2-pyridyl esters **146** as acylating agents and metal carboxylates as catalysts. $NiBr_2$/AgOPiv in MeCN or $CuCl_2$/AgOPiv in EtOAc and (*S*,*S*)- PhBox 140 as a chiral ligand gave the corresponding acylated diols **147** in generally good yields and enantioselectivities (Scheme 45). Asymmetric acylation of acyclic and cyclic *meso*-1,2-diols with aroyl and acyl chlorides has been carried out using enantiopure binuclear Zn(II) complex **148** as catalyst (Scheme 45) [99]. This complex was prepared by treating (1*R*,2*R*)-diphenylethylenediamine (DPEN) with 2-hydroxy-5-methyl-1,3-benzenedicarboxaldehyde and $Zn(OAc)_2$. The resulting monoesters **147** were obtained in high yields and moderate enantioselectivities.

alt-text: Scheme 45

Scheme 45

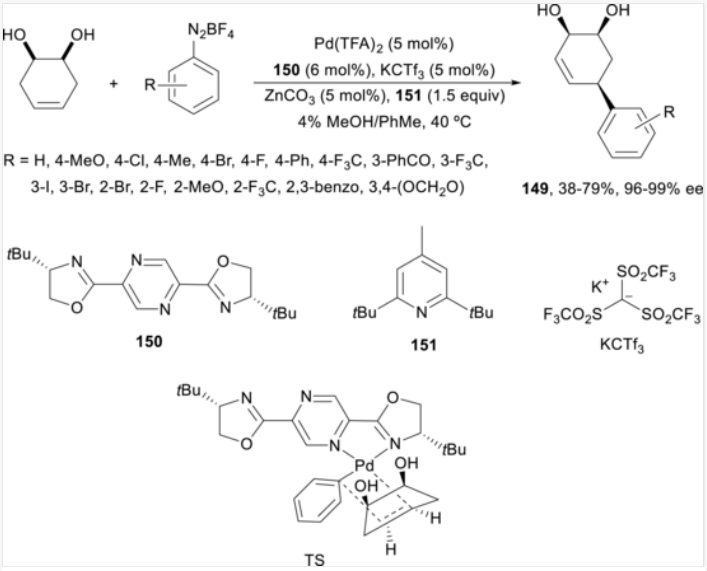


Metal-Catalyzed desymmetrization of *meso*-1,2-diols by an enantioselective acylation.

Correia, Hammond and co-workers [100] reported the desymmetrization of *cis*-cyclohex-4-ene-1,2-diol by an enantioselective Heck-Matsuda reaction with aryldiazonium tetrafluoroborates (Scheme 46). The arylation gave products **149** under mild reaction conditions in good yields and very high enantioselectivities using pyrabox (**150**) as chiral box ligand and catalytic amounts of $KCTf_3$ to promote the cationic reaction and DTBMP (**151**) in 4% MeOH in toluene. According to DFT calculations **TS** is the lowest in absolute energy, in which an *endo* hydroxy group orientation takes place with the aryl group *trans* to the oxazoline.

alt-text: Scheme 46

Scheme 46

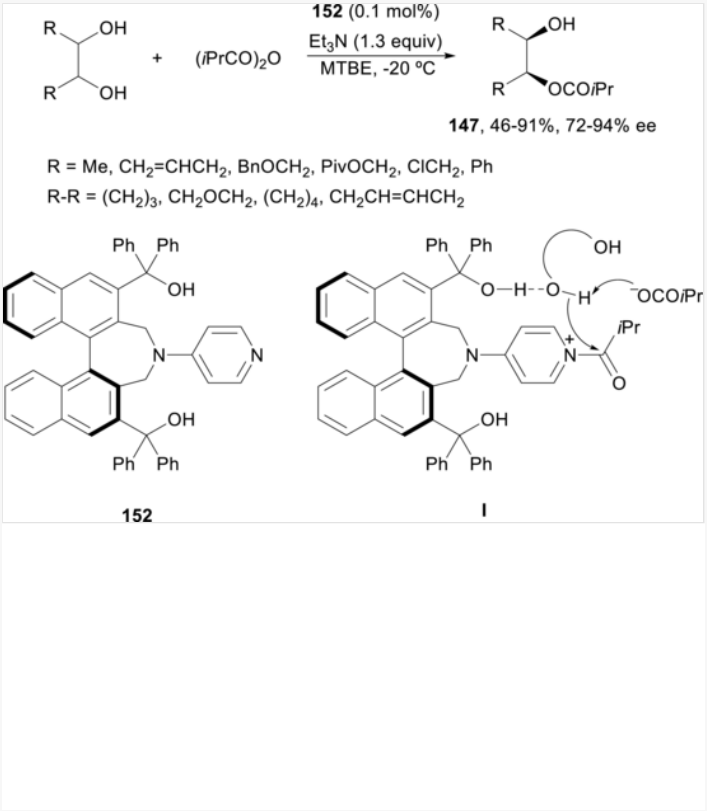


Pd-Catalyzed desymmetrization of *cis*-cyclohex-4-ene-1,2-diol by an enantioselective Heck-Matsuda arylation.

Organocatalyzed desymmetrization of 1,2-diols are focused on monoacylation reactions [14]. Enantiopure DMAP derivative **152** that contains a 1,1′-binaphthyl unit bearing at 3 and 3′ positions a tertiary alcohol is an efficient organocatalyst for the acylation of acyclic and cyclic *meso*-1,2-diols (Scheme 47) [101,102]. Monoacylated products **147** were mainly obtained in good yield and good enantioselectivities except in the case of cycloheptane- and cyclooctane-1,2-diols. Model **I** represents the hydrogen bonding interaction with the OH group and the attack to the *N*-acylpyridinium salt. This method is one of the most efficient protocols for the desymmetrization of 1,2-diols by acylation of one of the hydroxy groups.

alt-text: Scheme 47

Scheme 47



Organocatalyzed desymmetrization of acyclic and cyclic *meso*-1,2-diols by an enantioselective monoacylation.

Lipases have been used for desymmetrization of 1,2-diols either by acylation or by hydrolysis of their diacetates [25]. Oxidoreductases allowed the enantioselective formation of α-hydroxyketones [25]. Recently, butane-2,3-diol has been transformed into (−)-acetoin using two-enzyme system composed of butane-2,3-diol dehydrogenase and H_2O forming NADH oxidase by Wang and co-workers [103]. After optimization of the reaction conditions, 94% of *meso*-butane-2,3-diol was converted into (−)-acetoin isolated in 91% ee.

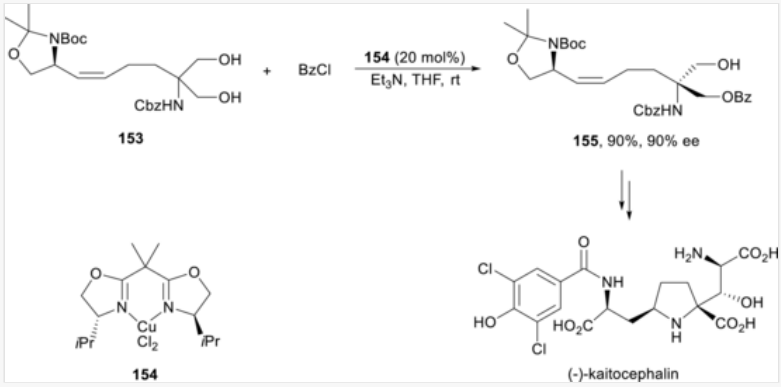
4.2 1,3-Diols

The desymmetrization of primary acyclic and cyclic 1,3-diols has been performed mainly by monoacylation reactions under metal catalysis [9,11,13] or by organocatalysis [5,12,21]. In the case of enzymatic processes mainly transesterification/hydrolysis catalyzed by lipases and oxidation reactions by oxidoreductases have been performed [13, 25].

Benzoylation of an acyclic 1,3-diol using a chiral bisoxazolidine-$CuCl_2$ catalyst was described by Trost and co-workers [104] for the synthesis of the macrolide (−)-18-*epi*-peloruside. The same desymmetrization strategy was pursued by Lee [105] for the synthesis of the natural product (−)-kaitocephalin, a glutamate receptor antagonist. The enantioselective desymmetrization of serinol **153** was carried out by benzoylation with benzoyl chloride using catalyst **154** (Scheme 48). Assuming that the substrate works as a tridentate ligand to form a pyramidal-shaped complex **I** the electrophilic Cu^{II} atom coordinates with benzoyl chloride from the open-bottoned face activating the benzoyl group. Monoester **155** was obtained in 90% yield and de, which was further transformed into (−)-kaitocephalin, a non-selective ionotropic glutamate receptor antagonist.

alt-text: Scheme 48

Scheme 48

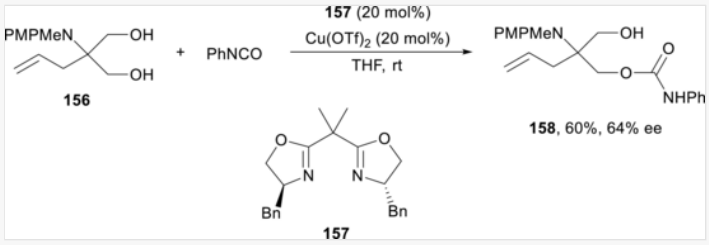


Cu-Catalyzed desymmetrization of acyclic diol **153** by an enantioselective benzoylation.

A similar catalyst formed by Bn-Box ligand **157** and $Cu(OTf)_2$ has been employed in the asymmetric carbamylation of diol **156** with phenyl isocyanate by Shimizu and co-workers (Scheme 49) [106]. The resulting carbamate **158** was obtained in 60% yield and 64% ee (absolute configuration not determined).

alt-text: Scheme 49

Scheme 49

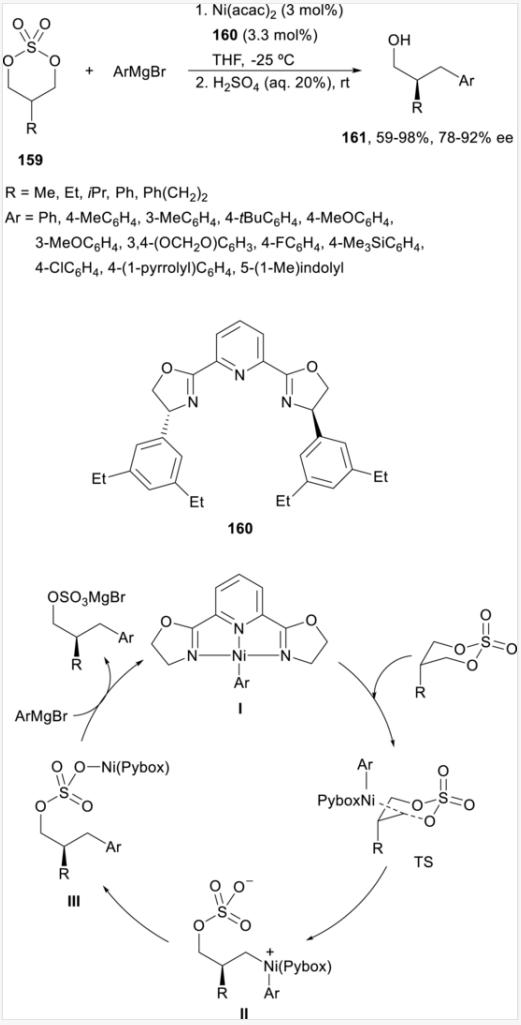


Cu-Catalyzed desymmetrization of acyclic 1,3-diol **156** by an enantioselective carbamylation.

Cyclic sulfates **159** derived from acyclic 1,3-diols were submitted to desymmetrization reaction by an asymmetric Kumada cross-coupling reaction by Morken and co-workers [107]. Aromatic Grignard reagents reacted with compounds **159** using $Ni(acac)_2$ and the chiral Pybox ligand **160** to provide alcohols **161** in good yields and enantioselectivities (Scheme 50). In consideration of mechanistic experiments it has been proposed that a catalytic cycle in which the sulfate with the C5 group in the axial position reacted by a S_N2-like oxidative addition with the Ni-complex **I** to give intermediate **II** through **TS**. Reductive elimination of **II** afforded the sulfate **III**, from which the catalyst **I** is regenerated by reaction with the Grignard reagent and the corresponding precursor of **161** is formed.

alt-text: Scheme 50

Scheme 50

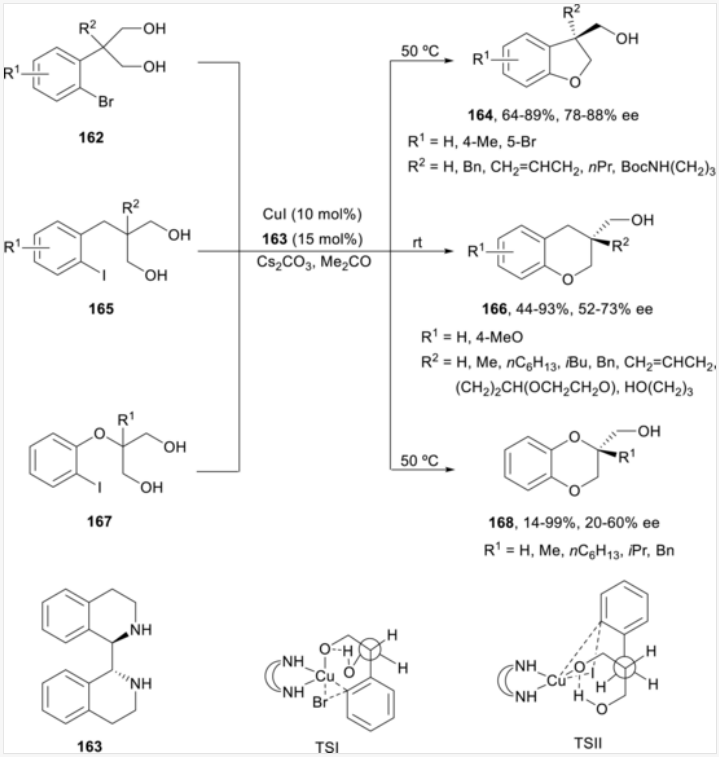


Ni-Catalyzed desymmetrization of 1,3-diol sulfates **159** by an enantioselective Kumada reaction.

Cai and co-workers have performed asymmetric desymmetrization of acyclic 1,3-diols by *O*-arylation under Pd- [108, 109] or Cu-catalyzed [110] processes. Recently, this Cu-catalyzed intramolecular *O*-arylation has been applied to the formation of chiral dihydrobenzofurans, chromanes and 1,4-benzodioxanes [111]. 1,3-Diols **162** were transformed into dihydrobenzofurans **164** using CuI and diamine **163** in good yields and enantioselectivities (Scheme 51). Homologous 1,3-diols **165** gave chromanes **166** and compounds **167** the corresponding 1,4-benzodioxanes **168**. DFT calculations for the cyclization of **162** a staggered conformation represented in **TSI** afforded (*S*)-**164**, whereas a less stable eclipsed conformation would give (*R*)-**164**. In the case of chromans **166**, in the cyclization of **165** through **TSII** the CH_2OH and the aryl group are in an anti position to provide the observed (*R*)-enantiomer, whereas a less stable gauche conformation of these groups would afford the (*S*)-configuration.

alt-text: Scheme 51

Scheme 51

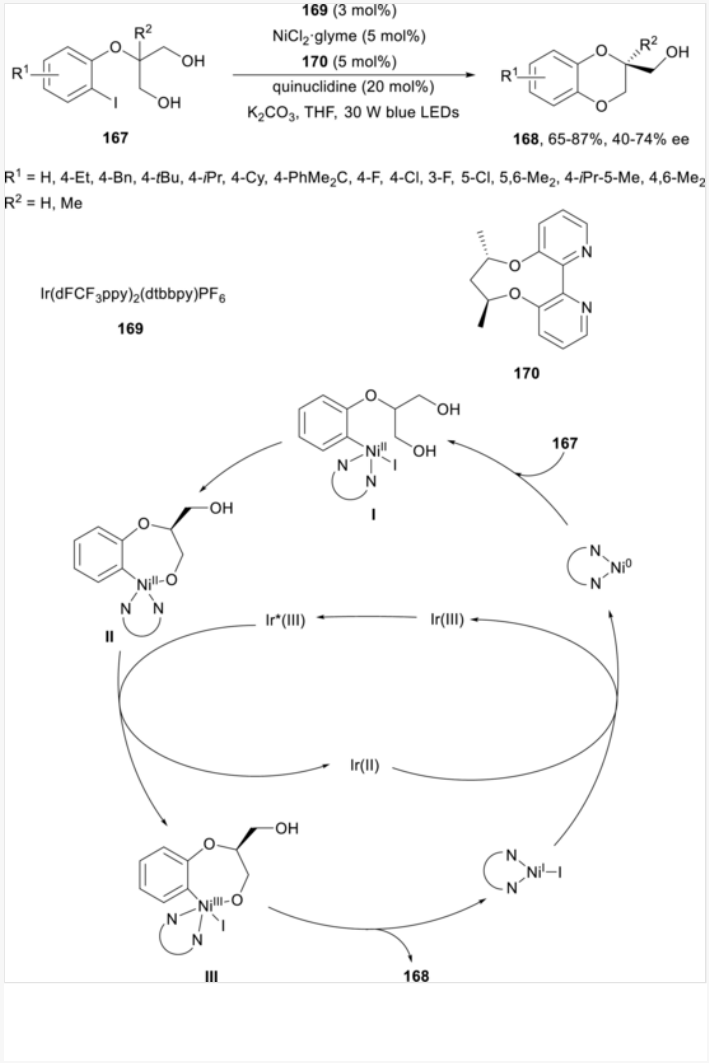


Cu-Catalyzed desymmetrization of 1,3-diols **162**, **165** and **167** by an enantioselective *O*-arylation.

Dual photoredox- and Ni-catalyzed desymmetrization of 2-(2-iodophenoxy)propane-1,3-diols **167** by C–O coupling has been reported by Xiao and co-workers [112]. Under visible light and Ir catalyst **169** the complex formed by $NiCl_2$ and the chiral ligand **170**, the corresponding 1,4-benzodioxanes **168** were obtained in good yields and moderate enantioselectivities (Scheme 52). The proposed mechanism involves firstly the oxidative addition of the chiral Ni(0) catalyst in the C–I bond to provide intermediate **I**, which by ligand exchange would produce the Ni(II) alkoxide **II**. Visible light irradiation of the Ir(III) photocatalyst would produce the long-lived photoexcited Ir*(III) state. The SET process between the Ni(II) intermediate **II** and the excited Ir*(III) photocatalyst would give intermediate **III** and the reduced Ir(II) species. Final reductive elimination furnished the product **168** and reduction of Ni(I) to Ni(0) by Ir(II) species.

alt-text: Scheme 52

Scheme 52

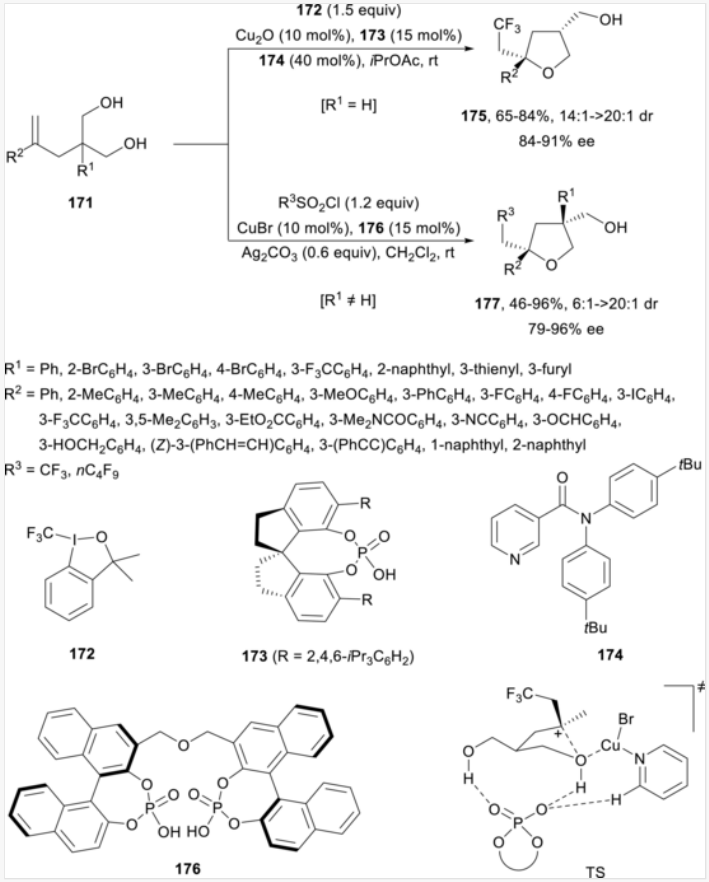


Photoredox and Ni-catalyzed desymmetrization of 1,3-diols **167** by an enantioselective C–O coupling.

Recently, Hong, Liu and co-workers [113] described the desymmetrization of olefinic 1,3-diols **171** with different radical precursors by enantioselective Cu(I)/chiral phosphoric acid (CPA) cooperative catalysis. Trifluoromethyl-substituted tetrahydrofurans **175** were obtained from diols **171** (R^1 = H) and Togni's reagent **172** in the presence of the chiral CuI/CPA catalyst **173** and *N,N*-bis(4-*tert*-butylphenyl)nicotinamide (**174**) for promoting stereoselectivity (Scheme 53). This methodology gave poor enantioselectivities with 1,3-diols **171** bearing a quaternary stereocenter ($R^1 \neq$ H). However, using trifluoromethanesulfonyl chloride as an alternative CF_3 source and in the presence of Ag_2CO_3 to quench the generated HCl, the corresponding tetrahydrofuran **177** ($R^1 = R^2$ = Ph; $R^3 = CF_3$) was isolated in 96% yield, 10:1 dr and 83% ee using the bisphosphoric acid **176** as chiral CPA. Perfluorobutanesulfonyl chloride was mainly used as radical precursor giving products **177** with high diastereo and enantioselectivity. Experimental and DFT studies supported the intermediacy of a radical **I**, which *via* a SET process gave the energetically most favorable **TS** due to π-π stacking between the phenyl and the pyridyl group and hydrogen bonding network stabilizing effects.

alt-text: Scheme 53

Scheme 53



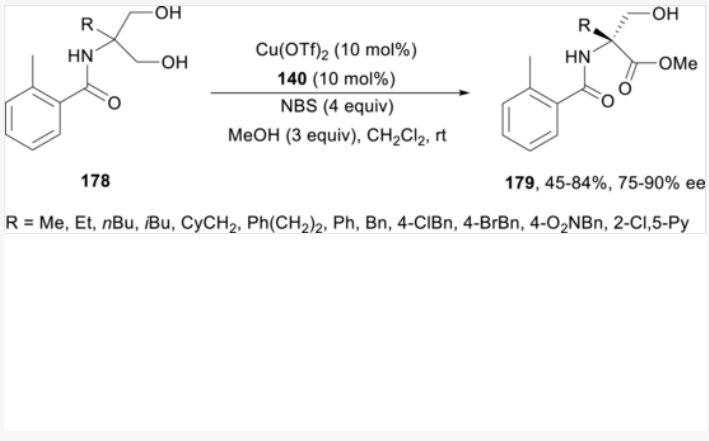
Cu-Catalyzed desymmetrization of olefinic 1,3-diols by an enantioselective C–O formation induced by radicals.

Enantioselective copper-catalyzed oxidative desymmetrization of acyclic 2-amino-1,3-diols **178** allowed the synthesis of α-substituted serine derivatives **179** [114]. The combination of $Cu(OTf)_2$ and (*R,R*)-PhBox (**140**) as catalyst, and *N*-bromosuccinimide (NBS) as oxidant and MeOH afforded products **179** working at room temperature under air (Scheme 54). This methodology for the synthesis of enantioenriched quaternary serine derivatives has been scaled up to 10 mmol scale and hydrolysis with aqueous 3 M HCl under reflux afforded (*R*)-α-methylserine hydrochloride in 93% yield.

Images are optimised for fast web viewing. Click on the image to view the original version.

alt-text: Scheme 54

Scheme 54

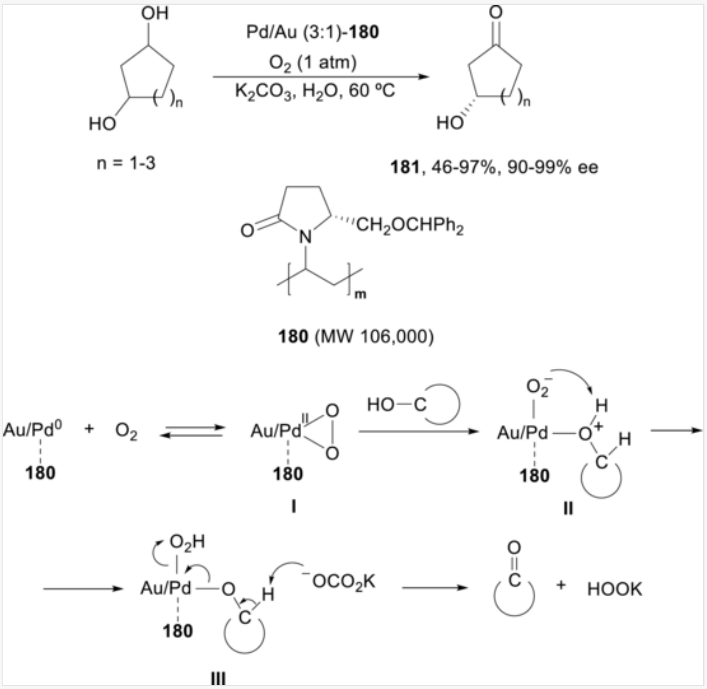


Cu-Catalyzed desymmetrization of 2-amino-1,3-diols by an enantioselective oxidation.

Cyclic 1,3-diols and 1,2-diols have been enantioselectively oxidized to β-hydroxy cycloalkanones and α-hydroxy cycloalkanones, respectively, using polymer-supported bimetallic nanoclusters by Hau and co-workers [115]. Poly-*N*-vinylpyrrolidinones containing a stereocenter at C5 of the pyrrolidinone ring, particularly **180** were used to stabilize Pd/Au nanoclusters. This supported catalyst allowed the enantioselective oxidation of 1,3-diols to hydroxy ketones **181** in moderate yields and excellent enantioselectivities (Scheme 55). In the proposed mechanism a peroxopalladium species **I** underwent diol attack leading to complex **II**, which by proton transfer gave intermediate **III**. Subsequent removal of hydrogen by K_2CO_3 afforded the ketone and hydrogen peroxide.

alt-text: Scheme 55

Scheme 55

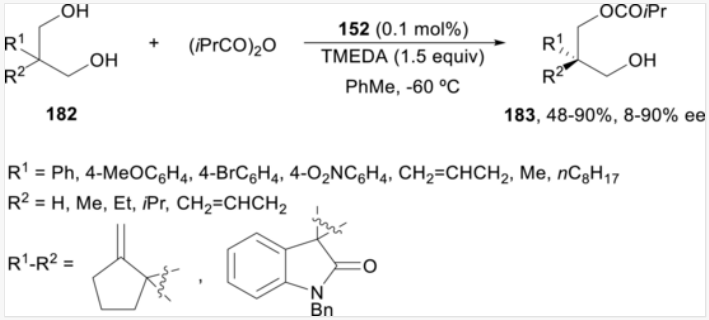


Au/Pd-Catalyzed desymmetrization of cycloalkane-1,3-diols by an enantioselective oxidation.

Organocatalyzed methods for 1,3-diols desymmetrization are based on acylation and oxidation reactions. Suga and co-workers used enantiopure DMAP derivative **152** (Scheme 47) not only for 1,2-diols [101,102] but also for the desymmetrization of 1,3-diols [116]. The acylation of 2,2-disubstituted 1,3-diols **182** with $(i\text{PrCO})_2O$ in the presence of **152** as catalyst and TMEDA occurred at −60 °C with good yields and modest to good enantioselectivities giving mainly monoprotected products **183** (Scheme 56).

alt-text: Scheme 56

Scheme 56

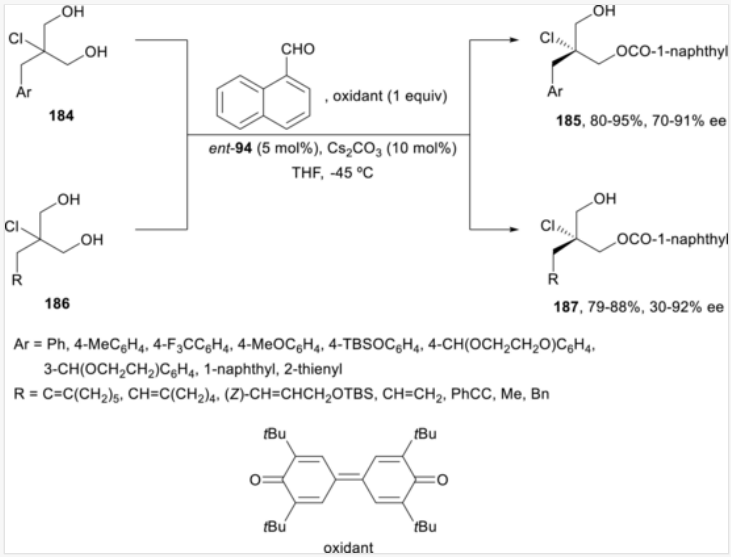


Organocatalyzed desymmetrization of 1,3-diols **182** by an enantioselective acylation.

Carbene-catalyzed desymmetrization [21,24] of 1,3-diols has been performed by Chi and co-workers [117] through an enantioselective Stetter reaction. 2-Chloro substituted 1,3-diols **184** were acylated with 1-naphthalenecarbaldehyde (**186**) using the chiral NHC precursor *ent*-**94** and the oxidant **187** to furnish products **185** (Scheme 57).

alt-text: Scheme 57

Scheme 57

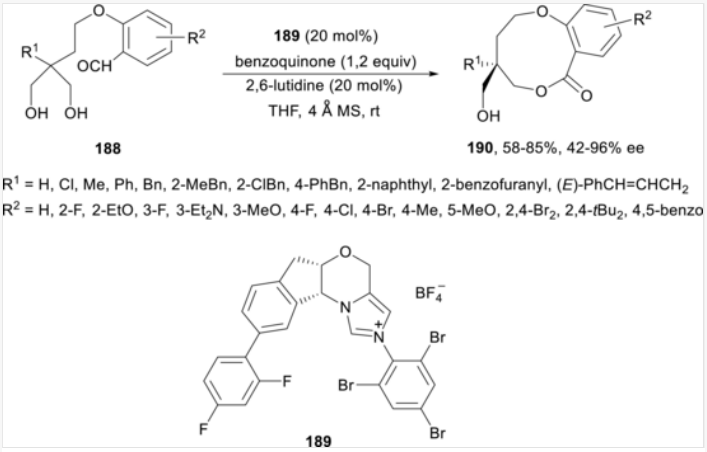


NHC-Catalyzed desymmetrization of 2-chloro-1,3-diols by an enantioselective Stetter reaction.

An intramolecular acylation reaction of 1,3-diols **188** catalyzed by a triazolium NHC precatalyst **189** has been reported by Wu and Wang [118]. Medium-size lactones **190** have been prepared in moderate to good yields and with high enantioselectivities (Scheme 58). A plausible mechanism involves the formation of the Breslow intermediate, which after oxidation gives the acylazolinium intermediate **I**. Subsequent lactonization of **I** would afford compounds **190**. This strategy has been successfully applied not only to nine-membered rings but also to eight, ten, eleven and twelve-membered lactones.

alt-text: Scheme 58

Scheme 58

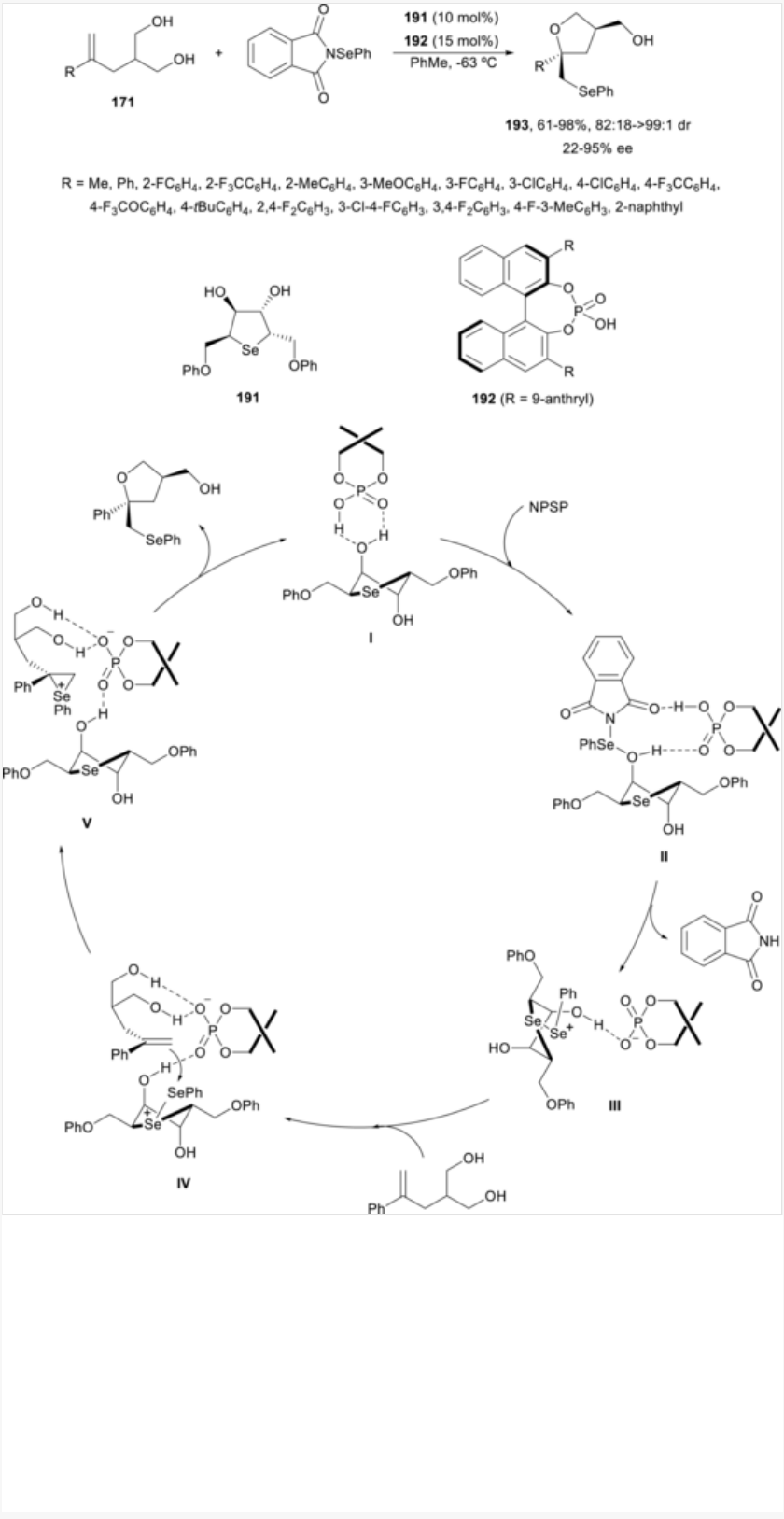


NHC-Catalyzed desymmetrization of 1,3-diols **188** by an enantioselective lactonization.

Selenoetherification of olefinic diols **171** (R = H) has been carried out using *N*-(phenylseleno)phthalimide (NPSP) as electrophilic selenylating agent and, as a matching catalyst pair, a chiral selenide **191** and a chiral BINOL-derived phosphoric acid **192** (Scheme 59) [119]. The corresponding phenylseleno-functionalized tetrahydrofurans **193** were obtained in good to excellent yields and dr and ee values. In the proposed catalytic cycle, based on experimental data and DFT calculations, a binuclear species formed by **191** and **192**, intermediate **I** was postulated according to mass spectrometry (*m/z* 1079.2263, negative mode). Then, intermediate **II** is formed by reaction of **I** with NPSP stabilized by intermolecular hydrogen bonds between **191** and **192** and between **192** and NPSP. This thermodynamically stable ternary complex **II**, with respect to the reactants, evolves to give phthalimide and a seleniranium-phosphate ion par (intermediate **III**). The addition of the olefinic diol **171** to intermediate **III** forms intermediate **IV** by transfer of $PhSe^+$ from catalyst **191** to olefin **171**. Subsequently, intermediate **V** is attacked by one of the hydroxy groups of the diol assisted by the phosphate as a Brønsted base to furnish product **193**.

alt-text: Scheme 59

Scheme 59

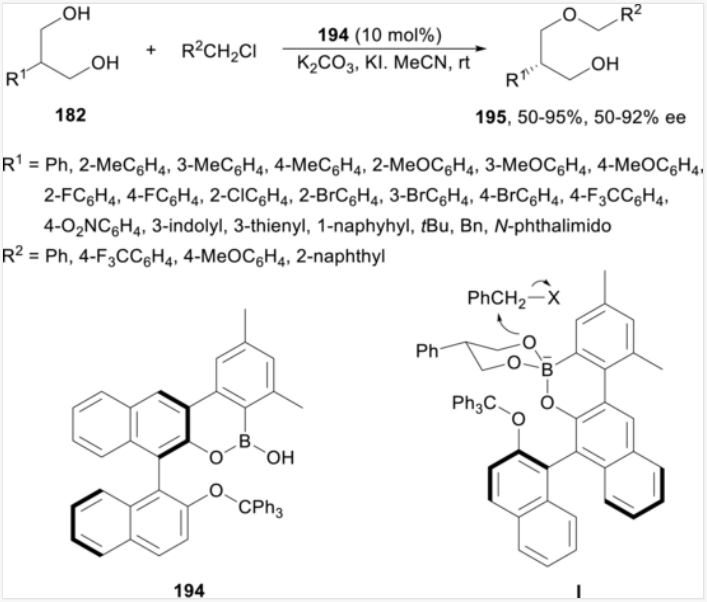


Chiral Lewis base-Brønsted acid catalyzed desymmetrization of olefinic 1,3-diols **171** by an enantioselective intramolecular selenoetherification.

Direct enantioselective *O*-arylation of 2-aryl-1,3-diols **182** (R^1 = aryl; R^2 = H) has been carried out by reaction with benzylic halides using a chiral hemiboronic acid **194** as catalyst by Hall and co-workers (Scheme 60) [120]. Using K_2CO_3 as base and KI, benzyl chlorides can be used giving products **195** in good yields and enantioselectivities. According to experimental results and DFT calculations a stereochemical model **I** for the monobenzylation was proposed where the trityl ether of the catalyst provides much greater steric hindrance and the electrophile approach takes place in the upper part of the chair-like anionic complex.

alt-text: Scheme 60

Scheme 60

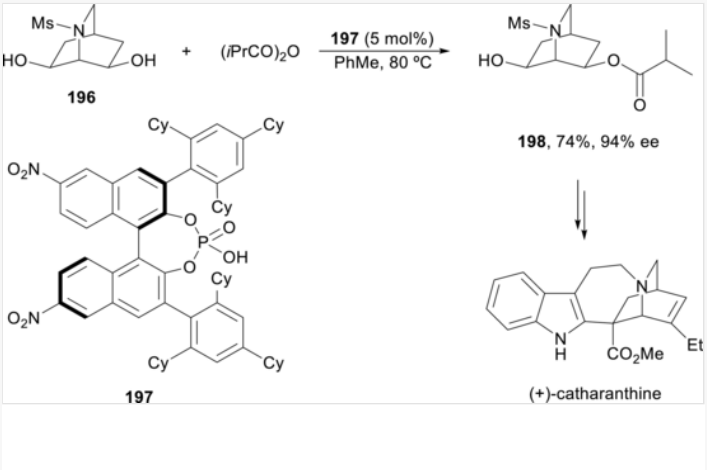


Hemiboronic acid-catalyzed desymmetrization of 1,3-diols **182** by an enantioselective benzylation.

Nemoto and co-workers [121] have performed the asymmetric formal synthesis of (+)-catharanthine, a member of the *Iboga* class of alkaloids with strong anticancer activity [122]. As key intermediate a *meso*-isoquinuclidine **196** possessing a 1,3-diol unit was submitted to desymmetrization using an enantioselective acylation catalyzed by a chiral phosphoric acid **197** (Scheme 61). The corresponding monoester **198** was obtained in 74% yield and 94% ee, which was further transformed in eight steps into a chiral synthetic intermediate [123] of (+)-catharanthine.

alt-text: Scheme 61

Scheme 61



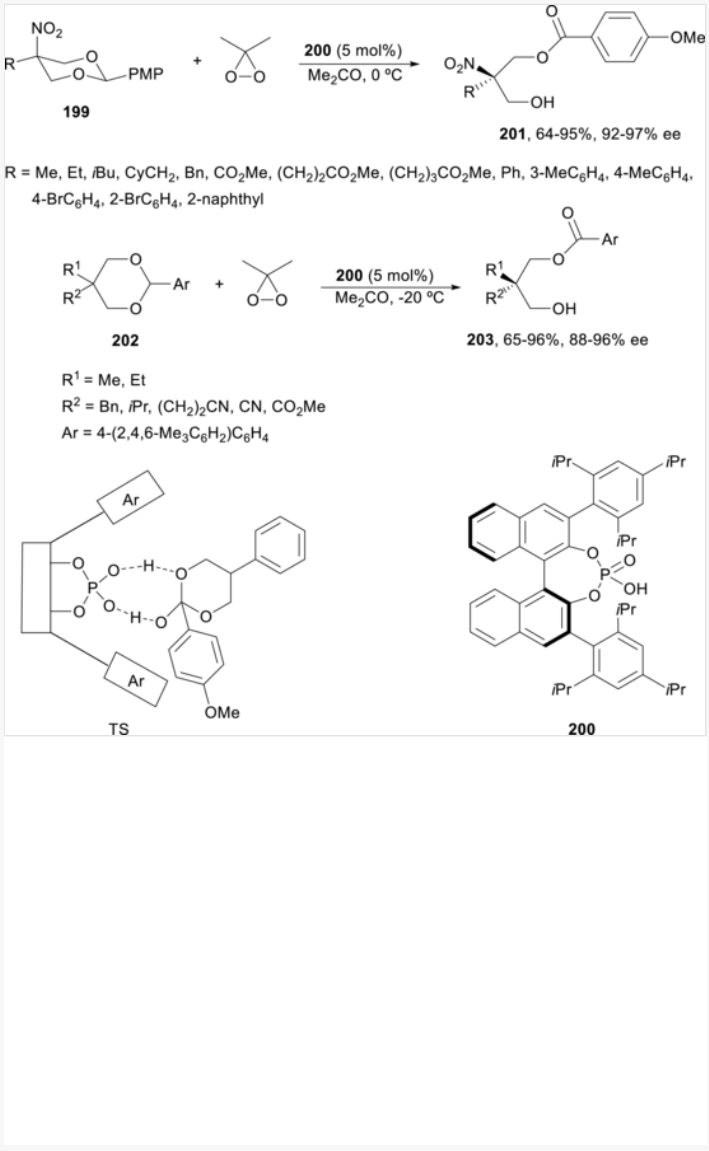
Phosphoric acid-catalyzed desymmetrization of 1,3-diol **196** by an enantioselective acylation.

Zeng and co-workers [124] reported a chiral phosphoric acid catalyzed desymmetrization of 2-mono and disubstituted 1,3-diols *via* oxidation cleavage of benzylidene acetals. More recently, the same group [125] performed the same process with 2-nitro-1,3-diols acetals **199** using (*S*)-TRIP (**200**) as CPA in the presence of dimethyldioxirane (DMDO) as oxidant (Scheme 62). The resulting monobenzoylated 2-nitro-1,3-diols **201** were obtained in good yields and enantioselectivities. This methodology has been applied to the formal synthesis of manzacidin A and C, isolated from sponges. DFT calculations were performed by Houk and Zeng groups [126] for the enantioselective desymmetrization

of 2-monoalkyl and dialkyl substituted 1,3-diol acetals **202**. From the theoretical studies it was found that 2,4,6-trimethylbiphenyl acetals gave products **203** with high enantioselectivity (Scheme 62). For the acetal **202** (R^1 = Ph; R^2 = H); Ar = PMP) it was found that **(*S*)-TS** is 2 kKcal/mol more stable than **(*R*)-TS** due to the more favorable aryl-aryl interactions. Additionally, the interaction between the phenyl group of **202** and the 2,4,6-triisopropylphenyl group of the catalyst also favors **(*S*)-TS**. In the case of 2-monoalkyl and dialkyl substituted 1,3-diol acetals **202** with 2,4,6-trimethylphenyl as protecting group the difference in energy between the (*R*) and (*S*)-transition states was 3.5 kcal/mol, imcreasing the enantioselectivity for these substrates.

alt-text: Scheme 62

Scheme 62

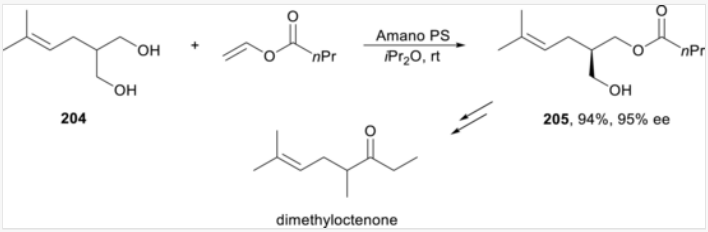


(*S*)-TRIP-catalyzed desymmetrization of 1,3-diols acetals **199** and **202** by an enantioselective oxidation.

Enzymatic desymmetrization of 1,3-diols has been carried out by an enantioselective transesterification, hydrolysis of diester derivatives and oxidation reactions [13,25]. Lipase-catalyzed acylation of 1,3-diols is a valuable methodology for the enantioselective synthesis of biologically active compounds. Kawasaki and co-workers [127] described that vinyl butyrate was a better acylation reagent than vinyl acetate for the enantioselective transesterification of 1,3-diol **204**. The highest enantioselectivity was achieved with lipase Amano PS in diisopropyl ether giving the (*R*)-enantiomer **205** in 95% yield (Scheme 63). This monoester **205** was used for the synthesis of both enantiomers of the citrus flavor 4,7-dimethyl-6-octen-3-one (dimethyloctenone) and its analogues.

alt-text: Scheme 63

Scheme 63

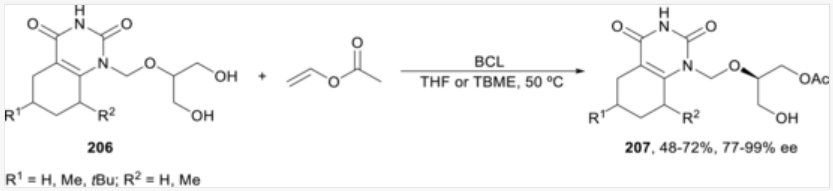


Lipase-biocatalyzed desymmetrization of 1,3-diol **204** by enantioselective transesterification.

Lipase Amano PS from *Burkholderia cepacia* (BCL) was the biocatalyst used for the monoacylation of pyrimidine acyclonucleosides **206** by Kolodziejska and co-workers [128]. Enzymatic transesterification of compounds **206** was carried out with vinyl acetate in a mixture of THF or TBME to give monoesters **207** in good enantiomeric and diastereomeric excess (Scheme 64). The same process was carried out with this lipase in ionic liquids. A mixture of [BMIM]PF_6/TBME (1:1) at 50 °C using vinyl butyrate as acylating agent gave the corresponding monoesters up to 93% ee [129].

alt-text: Scheme 64

Scheme 64

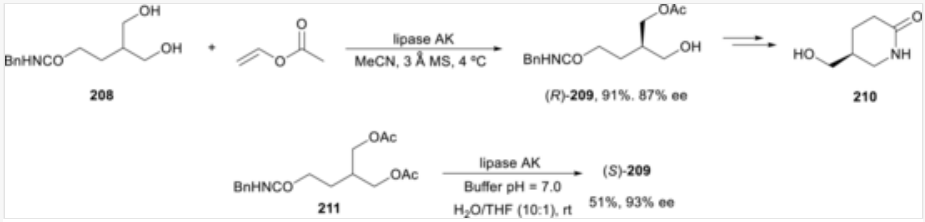


Lipase-biocatalyzed desymmetrization of diols **206** by an enantioselective transesterification.

Lipase AK (from *Pseudomonas fluorescens*, PFL) was the biocatalyst of choice for the acetylation of 1,3-diol **208** with vinyl acetate giving the monoester (*R*)-**209** in 91% yield and 87% ee (Scheme 65) [128]. This compound was transformed in six steps into piperidone **210** in 44% overall yield and 93% ee. The same enzyme was used for the hydrolysis of diacetate **211** which was transformed mainly into (*S*)-**209** in 51% yield and 93% ee.

alt-text: Scheme 65

Scheme 65



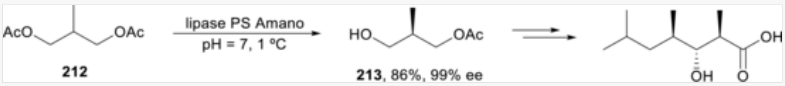
Lipase-biocatalyzed desymmetrization of 1,3-diol **208** by an enantioselective transesterification and of diacetate **211** by an enantioselective hydrolysis.

The fatty acid unit to build the *N*-terminus of the cyclodepsipeptides callipeltin A and homophymina B, isolated from marine sponges *Callipeta* sp. and *Homophymia* sp., respectively, has been synthesized by Tokairin and Konno [131]. Desymmetrization of the starting 2-methyl-1,3-propanediol was first attempted with vinyl acetate and lipase AK (PFL), which gave monoacetate (−)-**213** in 40% yield and 98% ee. The desired enantiomer (+)-**213** was obtained by hydrolysis of diacetate **212** with lipase PS at pH = 7 (phosphate buffer) in 86% yield and 99% ee (Scheme 66).

Images are optimised for fast web viewing. Click on the image to view the original version.

alt-text: Scheme 66

Scheme 66



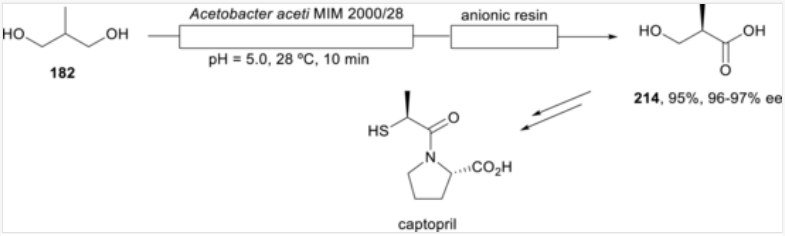
Lipase-catalyzed desymmetrization of diacetate **212** by an enantioselective hydrolysis.

Oxidation of 1,3-diols **182** (R^2 = H) by *Acetobacter aceti* MIM 2008/28 to β-hydroxy acid **214** was carried out by Brenna and co-workers [132]. The corresponding enantioenriched acids were obtained in aqueous medium at pH = 5.0 in moderate to good yields and enantioselectivities. This oxidation reaction was carried out in a continuous flow reactor by Tamborini and co-workers [133] to synthesize **214** in 95% yield and 96–97% ee, which is a precursor of the angiotensin converting enzyme (ACE) inhibitor captopril, an antihypertensive drug (Scheme 67).

Images are optimised for fast web viewing. Click on the image to view the original version.

alt-text: Scheme 67

Scheme 67

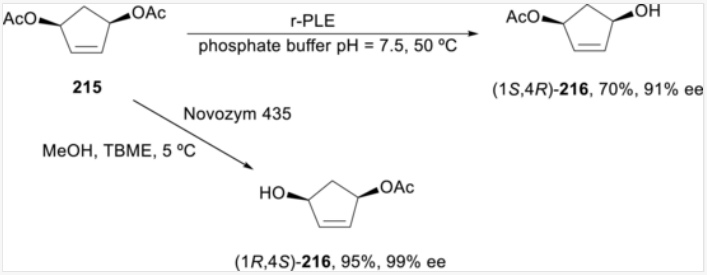


Enzyme-catalyzed desymmetrization of diol **182** by an enantioselective oxidation.

Chiral monoacetylated *cis*-2,4-dihydrocyclopent-2-ene (**216**) is an important building block for the synthesis of prostaglandins, some antibiotics and natural cyclopentanoids [25]. Enzymatic process with lipases involved acylation of the corresponding *meso*-diol or enantioselective hydrolysis or alcoholysis of its diacetate **215** affording the corresponding enantiomers when two enzymes are used with opposite stereopreference. Recombinant pig liver stearase (PLE) was used for the desymmetrization of diacetate **215** in multigram scale to afford (1*S*,4*R*)-**216** after crystallization in 99% ee and 40% yield (Scheme 68) [134]. For the transesterification of **215** with MeOH an inmobilized lipase from *Candida antartica* (Novozym® 435) gave (1*R*,4*S*)-**216** in 95% yield and 99% ee. The enzyme was reused up to 10 cycles without changes in its catalytic activity [135].

alt-text: Scheme 68

Scheme 68

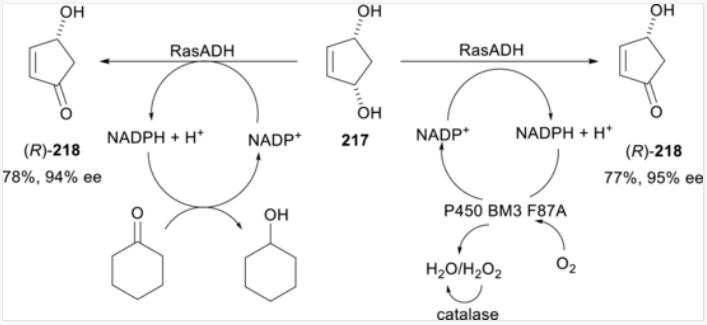


Lipase-catalyzed desymmetrization of diacetate **215** by an enantioselective hydrolysis or transesterification.

Starting from *meso*-diol **217** oxidative desymmetrization was carried out with crude lysate of cells *Ralstonia* sp. (RasADH) to give (*R*)-4-hydroxycyclopentenone **218** in 78% yield and 94% ee (Scheme 69) [136]. In this case cyclohexanone was used for $NADP^+$ regeneration. When the enzyme coupled P450 BM3 F87A-base cofactor was used a regeneration system (*R*)-**218** was obtained in 77% yield and 95% ee [137]. This 4-hydroxy-2-cyclopentenone was used for the preparation of travoprost, an analogue of PGF_2a used as antiglaucoma drug [136].

alt-text: Scheme 69

Scheme 69



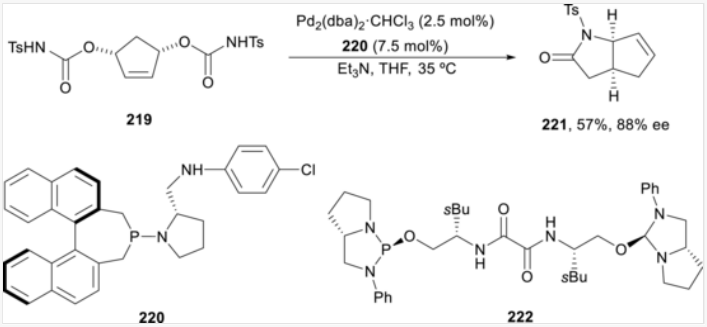
RasADH-catalyzed desymmetrization of 1,3-diol **217** by an enantioselective oxidation.

Palladium-catalyzed asymmetric allylic substitution has been used for desymmetrization of *O*-protected diol systems. Biscarbamate **219** was transformed into product (*S*,*R*)-**221** by intramolecular attack in 57% yield and 88% ee using chiral ligand **220** (Scheme 70) [138]. The same process was carried out using as a chiral ligand an oxalamide-based bisdiamidophosphite **222** which afforded **221** in 81% yield and 83% ee [139].

Images are optimised for fast web viewing. Click on the image to view the original version.

alt-text: Scheme 70

Scheme 70



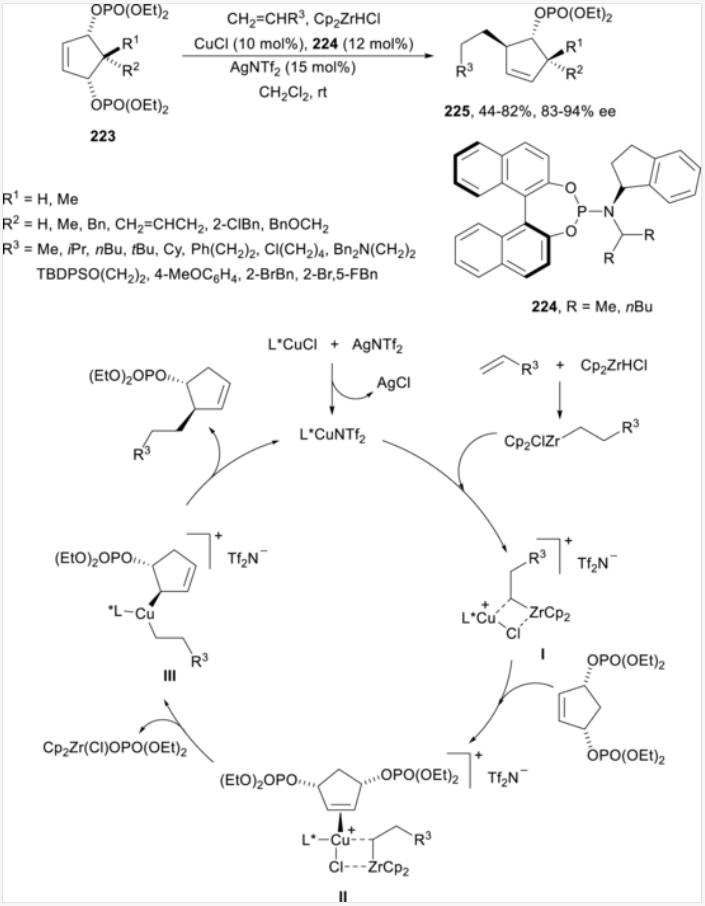
Pd-Catalyzed of 1,3-diol carbamate **219** by an enantioselective intramolecular allylic substitution.

Fletcher and co-workers [140] applied a copper-catalyzed allylic substitution for desymmetrization of 1,3-diol phosphates **223** (Scheme 71). In this case, alkylzirconocenes prepared *in situ* by hydrozirconation of alkenes were used as nucleophiles and chiral phosphoramidites **224** as ligands to furnish products **225** in good yields and stereoselectivities. In the postulated catalytic cycle the bimetallic species **I** can be formed, which by coordination to the bisphosphate provided intermediate **II**. By a displacement reaction of **II** a Cu(III) σ-allyl species **III** was formed, which underwent reductive elimination to give products **225** with regeneration of the Cu-phosphoramidite catalyst. The same group performed desymmetrization of *meso*-bisphosphates **223** *via* Rh-catalyzed asymmetric allylic arylation using arylboronic acids [141]. In this case (*S*)-DM-Segphos was used as a chiral ligand and $[Rh(cod)(OH)]_2$ as catalyst giving products type **225** in 12–77% yield, 3:1–8:1 dr and 94->99% ee.

Images are optimised for fast web viewing. Click on the image to view the original version.

alt-text: Scheme 71

Scheme 71



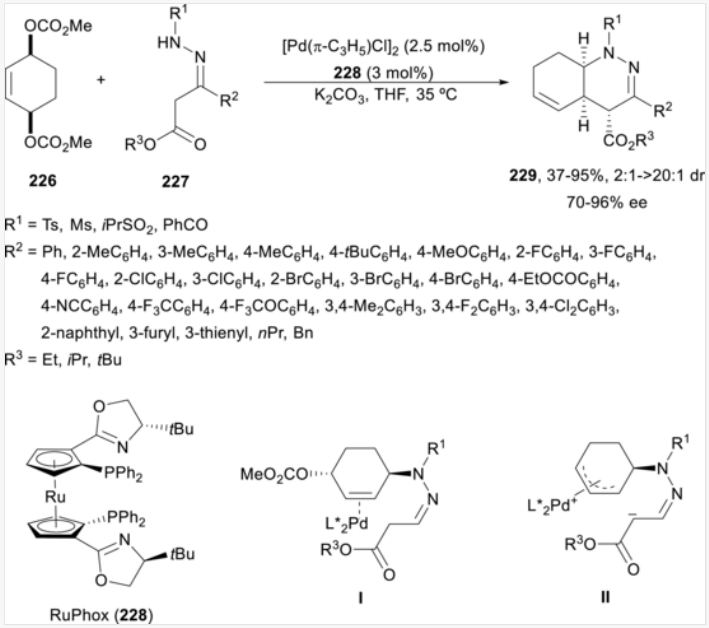
Cu-Catalyzed desymmetrization of 1,3-diol phosphates **223** by an enantioselective allylic substitution with alkylzirconocenes.

4.3 Other diols

The desymmetrization of *meso*-2,4-dihydroxycyclohex-2-ene has been achieved by Liu and co-workers [142] by enantioselective Pd-catalyzed allylic substitution using its dicarbonate **226** (Scheme 72). β-Hydrazino carboxylic esters **227** were used as nucleophiles and RuPhox (**228**) as a chiral ligand affording hexahydrocinnoline derivatives **229** up to 95% yield, >20:1 dr and 96% ee. Chiral cinnolines are structural motifs in numerous medicinally important compounds, such as cinoxacin, cinnopentazone, analgesics, etc. In the proposed reaction mechanism the nitrogen attacks to the π-allyl intermediate instead of the carbon attack giving intermediates **I** and **II**, which after intramolecular substitution provided compounds **229**.

alt-text: Scheme 72

Scheme 72

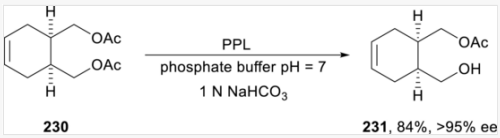


Pd-Catalyzed desymmetrization of *meso*-2,4-dihydroxycyclohex-2-ene carbonate **226** by an enantioselective allylic substitution with **227**.

Enzymatic desymmetrization of *meso*-diacetate **230** has been carried out by Ghosh and Sarkar by hydrolysis with PPL at pH = 7 in the presence of $NaHCO_3$ to neutralize the acetic acid released in the reaction (Scheme 73) [143]. This process was performed in 51 g scale resulting alcohol **231** in 84% yield and >95% ee. This monoacetate **231** was converted into yohimbine alkaloids (−)-alloyohimbane and (−)-yohimbane.

alt-text: Scheme 73

Scheme 73

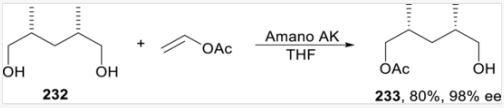


PPL-Catalyzed desymmetrization of *meso*-diacetate **230** by an enantioselective hydrolysis.

The *meso*-1,5-diol **232** has been monoacetylated with vinyl acetate using lipase Amano AK to provide compound **233** in 80% yield and 98% ee (Scheme 74) [144]. This monoacetate **233** has been used as starting material for the formal total synthesis of the marine natural product amphidinolide Q [145] with potent cytotoxicity and the macrolide framework of the antibiotic aldgamycin-M [146].

alt-text: Scheme 74

Scheme 74

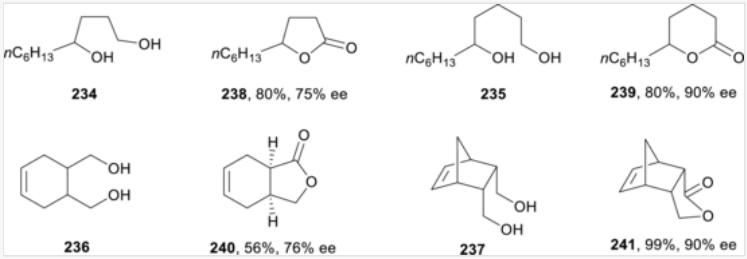


Lipase-catalyzed desymmetrization of *meso*-1,5-diol **232** by an enantioselective acylation.

Rhodococcus erythropolis DSM 44534 cells have been used to oxidize decane-1,4-diol (**234**) and decane-1,5-diol (**235**) into the corresponding optically active lactones **238** and **239**, respectively (Fig. 2) [147]. The corresponding γ-lactone **238** was obtained in 75% ee, whereas the δ-decalactone **239** in 90% ee. In addition, 1,4-diol **236** was oxidized to lactone **240** in 56% yield and 76% ee, whereas 1,4-diol **237** gave quantitative bicyclic lactone **241** in 90% ee. The process was carried out using phosphate buffer at 30 °C.

alt-text: Fig. 2

Fig. 2

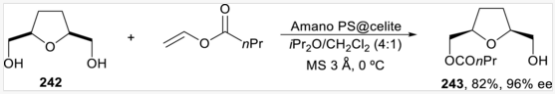


Rhodococcus erythropolis DMS 44534-catalyzed desymmetrization of diols **234–237** by an enantioselective oxidation to lactone **238–241**.

Both enantiomers of monoester **243** have been obtained by desymmetrization of *meso*-diol **242**, a renovable building block, and its dibutyrate ester through acylation and hydrolysis, respectively [148]. The acylation with vinyl acetate was performed with lipase from *Burkholderia cepacia* (Amano PS) immobilized on Celite (Scheme 75). When the reaction time was prolonged to 20 h product **243** was isolated in 72% yield and 99% ee.

alt-text: Scheme 75

Scheme 75



Lipase-catalyzed desymmetrization of 1,6-diol **242** by an enantioselective acylation.

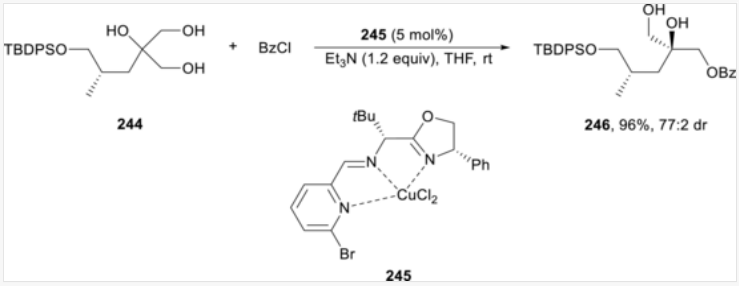
4.4 Polyols

1,2,3-Triols have been enantioselectively desymmetrized under metal-catalysis, organocatalysis and using bioenzymatic processes [12,25]. Some recent developments follow.

Desymmetrization of triol **244** has been carried out under Cu-catalyzed benzoylation using **245** as catalyst by Lu, Kang and co-workers [149] (Scheme 76). The resulting monobenzoate **246** was obtained in 96% yield mainly as one diastereomer, which was further employed for the synthesis of the C11–C24 fragment of inostamycin A with potent cytotoxic activity.

alt-text: Scheme 76

Scheme 76

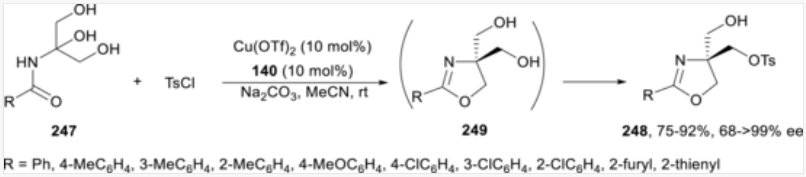


Cu-Catalyzed desymmetrization of triol **244** by an enantioselective benzoylation.

Onamura and co-workers [150] studied the Cu-catalyzed desymmetrization of amidotriols **247** by intramolecular cyclization followed by sulfonylation to provide oxazolines **248** (Scheme 77). In this case, $Cu(OTf)_2$ and (*R*,*R*)-PhBox (**140**) were used as catalyst under mild reaction conditions. From control experiments it was deduced that desymmetrization occurred on the resultant oxazoline diols **249** and in addition a kinetic resolution process was involved in the sulfonylative asymmetric desymmetrization step, which increased the enantiopurities of products **248**. The possible mechanism is similar than it was depicted in Scheme 48.

alt-text: Scheme 77

Scheme 77

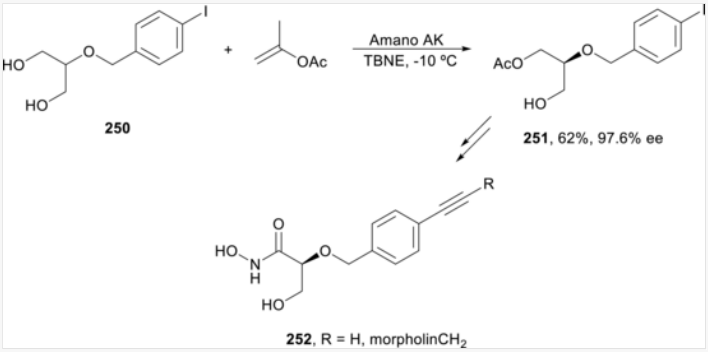


Cu-Catalyzed desymmetrization of amidotriols **247** by an enantioselective tosylation.

Glycerol was transformed into diol **250**, which was submitted to Amano AK lipase acylation with isopropenyl acetate to provide monoacetate **251** at −10 °C in TBME in 62% yield and 97.6% ee (Scheme 78) [151]. This compound **251** was transformed into glyceric hydroxamic acids **252** which showed antibacterial activity against two *Scherichia coli* strains.

alt-text: Scheme 78

Scheme 78

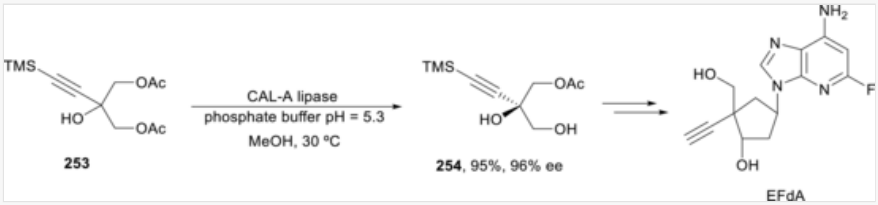


Lipase-catalyzed desymmetrization of glicerol derivative **250** by an enantioselective acetylation.

Lipase A from *C. antartica* (CAL-A) was employed as biocatalyst for the desymmetrization of diacetate **253** by hydrolysis at pH = 5.3 in MeOH (Scheme 79) [152]. The resulting monoacetate (*R*)-**254**was obtained in 95% yield and 96% ee and was further transformed into EFdA, a potent anti-HIV nucleoside.

alt-text: Scheme 79

Scheme 79

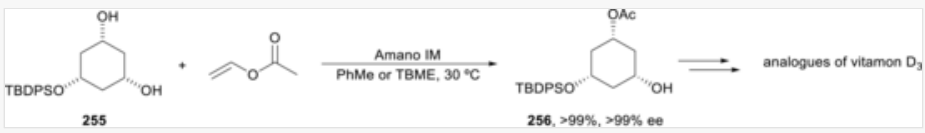


CAL-A Lipase-catalyzed desymmetrization of diacetate **253** by an enantioselective hydrolysis.

Desymmetrization of 1,3,5-cyclohexanetriol is a key strategy to control the stereochemistry of ring A for the synthesis of vitamin D_3 analogues [153]. In the case of monosilylated all-*cis*-1,3,5-cyclohexanetriol **255**, the monoacylation was performed enantioselectively with vinyl acetate by lipase from *Pseudomonas cepacia* inmobilized on diatomaceous earth (Amano IM) in toluene or TBME [153]. The resulting monoacetate **256** with (1*R*,3*S*,5*S*)-configuration was obtained in >99% yield and >99% ee (Scheme 80).

alt-text: Scheme 80

Scheme 80

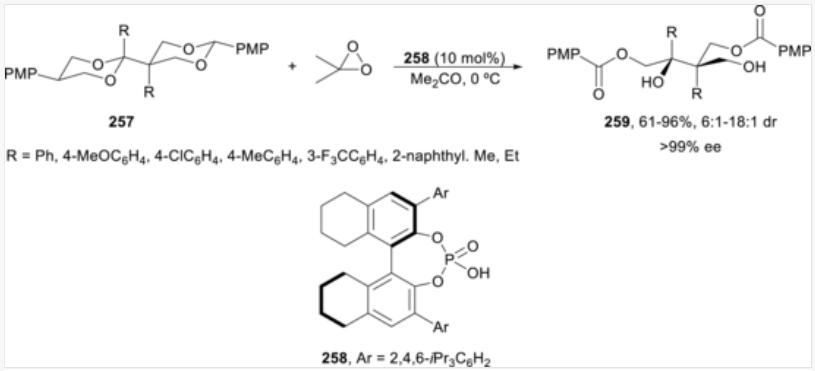


Lipase-catalyzed desymmetrization of silylated 1,3,5-cyclohexanetriol **255** by an enantioselective acetylation.

Tetrols have been transformed into benzylidene acetals **257** which could be desymmetrized by oxidation with DMDO in the presence of H8-TRIP (**258**) as chiral phosphoric acid (Scheme 81) [154]. Products **259** were obtained in high yields, diastereo and enantioselectivities under mild reaction conditions.

alt-text: Scheme 81

Scheme 81

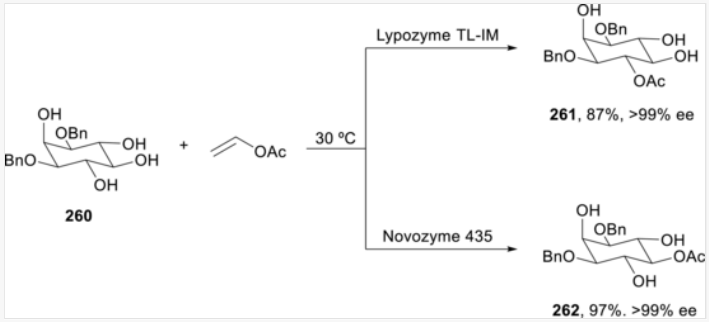


Phosphoric acid-catalyzed desymmetrization of tetraol acetals **257** by an enantioselective oxidation.

myo-Inositol derivative **260** has been submitted to lipase desymmetrization by formation of the chiral acetate **261** (Scheme 82) [155]. Among the lipases tested, Lipozyme RM-IM and TL-IM were effective for the acetylation of the 6-hydroxy group in high conversion and ee. Conversely, Novozyme 435 and Lipomod 34 PP afforded the 5-*O*-acetylated product **262**. TL-IM lipase was reused seven times without detriment of the biocatalytic activity.

alt-text: Scheme 82

Scheme 82



Lipase-catalyzed desymmetrization of 1,3-di-*O*-benzyl-*myo*-inositol **260** by an enantioselective acetylation.

5 Ketones and diketones

In this Section, desymmetrization of cyclohexanones, cyclohexadienones, cycloalkanediones, cyclopenten-1,3-diones and 1,4- and 1,5-diketones will be considered. Enantioselective desymmetrization of cyclobutanones, mainly based on ring expansion reactions catalyzed by Rh, Ni and Pd complexes, organocatalyzed and biocatalyzed methods has been recently reviewed by Sietmann and Wiest [156].

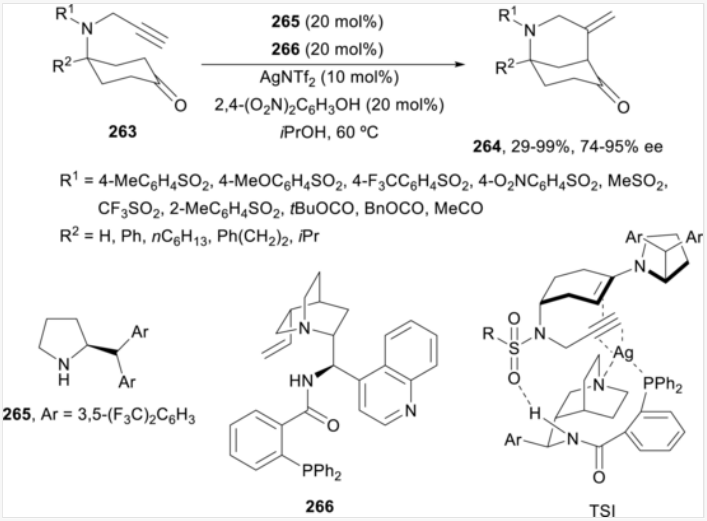
5.1 Cyclohexanones

Desymmetrization of 4-substituted cyclohexanones has been mainly carried out by metal catalysis and organocatalytic methodologies based on intra- and intermolecular α-alkylations and aldol reactions. Paton, Dixon and co-workers [157] developed a Ag/amine co-catalyzed desymmetrization of 4-propargylaminocyclohexanones **263** for the direct synthesis

of 2-azabicyclo[3.3.1]nonanes **264** (Scheme 83). The secondary amine **265** activates the ketone functionality by transient enamine formation and the *Cinchona* alkaloid-derived aminophosphine ligand **266**, for the Ag(I) salt activates the alkyne moiety giving after intramolecular cyclization compounds **254**, in general, in good yields and enantioselectivities. Based on DFT calculations simplified **TS** was shown to be the less energetic with a shorter NH···O hydrogen bond between the sulfonate and the amidic N–H group of the aminophosphine **266**. The *s-cis* enamine is the preferred conformation in which the sterically demanding diarylmethyl group is at the upper position.

alt-text: Scheme 83

Scheme 83

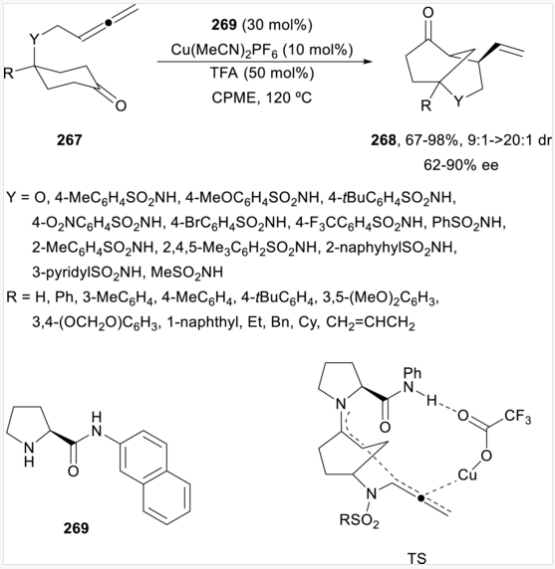


Ag- and amine co-catalyzed desymmetrization of 4-propargylaminocyclohexanones **263** by an enantioselective cycloisomerization.

The same group [158] studied the dual catalytic desymmetrization of allene-tethered cyclohexanones **267** to afford aza- and oxabicyclo[3.3.1]nonan-2-ones **268** (Scheme 84). In this case, prolinamide **269** and a Cu-salt were used as catalysts in the presence of trifluoroacetic acid at 120 °C. This cyclization took place *via* enamine catalysis and by activation of the allene unit by the copper salt. DFT studies into this morphan core synthesis elucidated that the reaction proceeds through a key strain-minimized **TS** in which the prolinamide and the copper catalyst were linked by a trifluoroacetate bridge.

alt-text: Scheme 84

Scheme 84



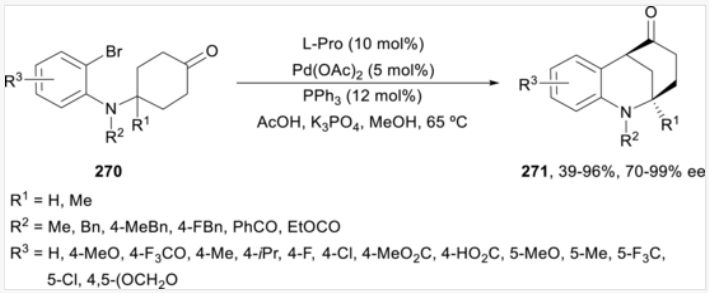
Cu- and amine-catalyzed desymmetrization of allene-tethered 4-substituted cyclohexanones **267** by an enantioselective intramolecular cyclization.

Pd/enamine cooperative catalysis allowed desymmetrization of 4-(2-bromoarylamino)cyclohexanones **270** to provide optically active morphan derivatives **271** in good yields and enantioselectivities (Scheme 85) [159]. The α-arylation/cyclization of the cyclohexanone unit took place through the corresponding enamine intermediate using L-Pro as chiral organocatalyst.

Images are optimised for fast web viewing. Click on the image to view the original version.

alt-text: Scheme 85

Scheme 85

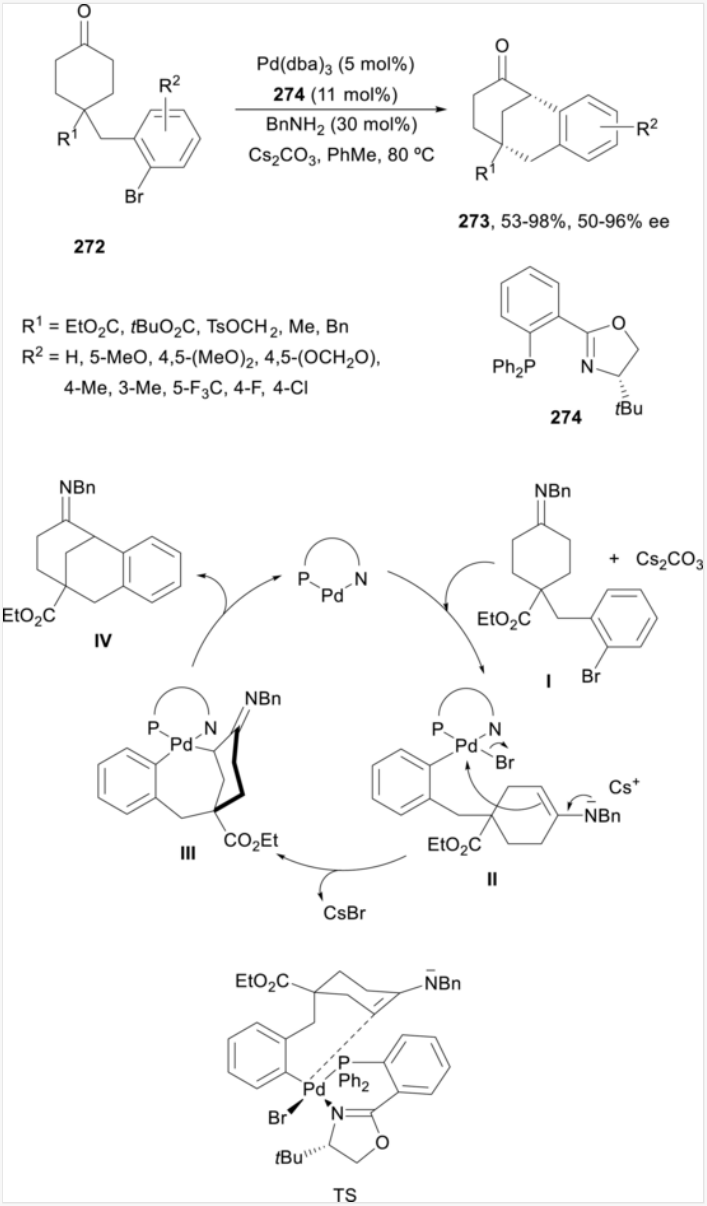


Pd- and amine-catalyzed desymmetrization of 4-(2-bromoarylamino)cyclohexanones **270** by an enantioselective α-arylation-cyclization.

Intramolecular coupling of 4,4-disubstituted cyclohexanones **272** under amine/Pd co-catalysis afforded bicyclo[3.3.1]nonanes **273** in good yields and enantioselectivities (Scheme 86) [160]. $Pd_2(dba)_3$ with (*S*)-*t*BuPhox (**274**) as a chiral ligand and benzylamine acted as dual catalysts allowing the α-alkylation of cyclohexanones **272** using aryl, heteroaryl, alkenyl bromides and triflates. The proposed catalytic cycle involves the oxidative addition of the Pd complex to the aryl bromide **I** to form intermediate **II**. After nucleophilic attack of the enamine to the Pd–Br bond, palladacycle **III** will be formed and after reductive elimination to give **IV**, which by imine hydrolysis provided product **273**. The presence of benzylamine dramatically accelerates the initial rate of the reaction. DFT calculations support the formation of **TS**, which explains the observed enantioselectivity avoiding steric interactions between the benzyl group of the enamine and the ligand. The reaction has been carried out in gram-scale for **273** with $R^1 = EtO_2C$ and $R^2 = H$, which was further transformed into different valuable chiral building blocks including dihydronaphthalenes, ring-fused indoles, lactones, tetralones and 6,6,5-tricycles.

alt-text: Scheme 86

Scheme 86

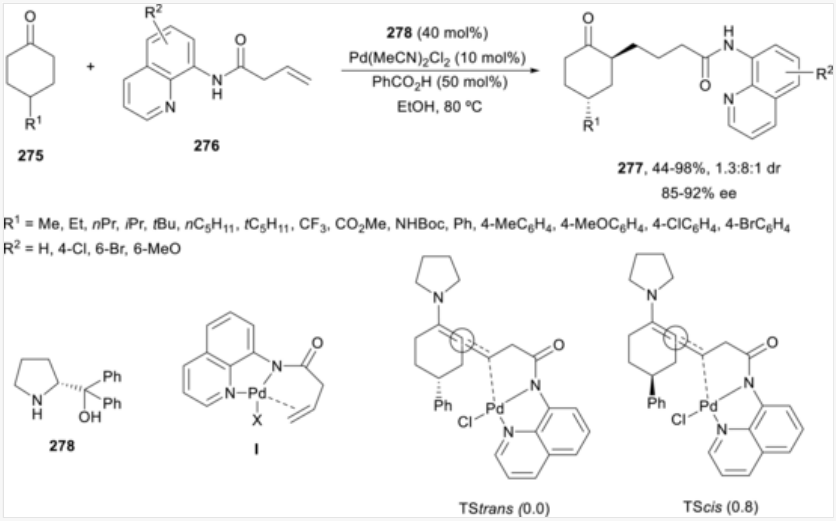


Pd and amine co-catalyzed desymmetrization of cyclohexanones **272** by an enantioselective intramolecular coupling.

Amine/Pd(II) cooperative catalysis has been applied to desymmetrization of 4-substituted cyclohexanones **275** by enantioselective addition to functionalized alkenes **276** (Scheme 87) [161]. In the presence of diphenylprolinol **278** as chiral amine and $Pd(MeCN)_2Cl_2$ as synergetic catalysts, the γ-addition products **277** were obtained in good yields and moderate diastereo- and enantioselectivities. By formation of intermediate *syn*-enamines the nucleophilicity of the α-carbon of the ketones was enhanced, whereas the amide group activates the alkene coordinating the Pd to form palladacycle **I**, which approached at the *Si* face of the enamine. **TS** *trans* and **TS** *cis* have similar relative energies with a difference of 0.8 kKcal/mol, which determine the moderate diastereomeric ratio according to DFT calculations. Two scale-up procedures were performed with butenamide **276** (R^2 = H) and two cyclohexanones **275** (R^1 = 4-$MeOC_6H_4$, Me) and the resulting products were transformed into other building blocks. This desymmetrization was also performed with 3-phenylcyclobutanone and butenamide **276** (R^2 = H) with moderate results (56% yield, >20:1 dr and 73% ee).

alt-text: Scheme 87

Scheme 87

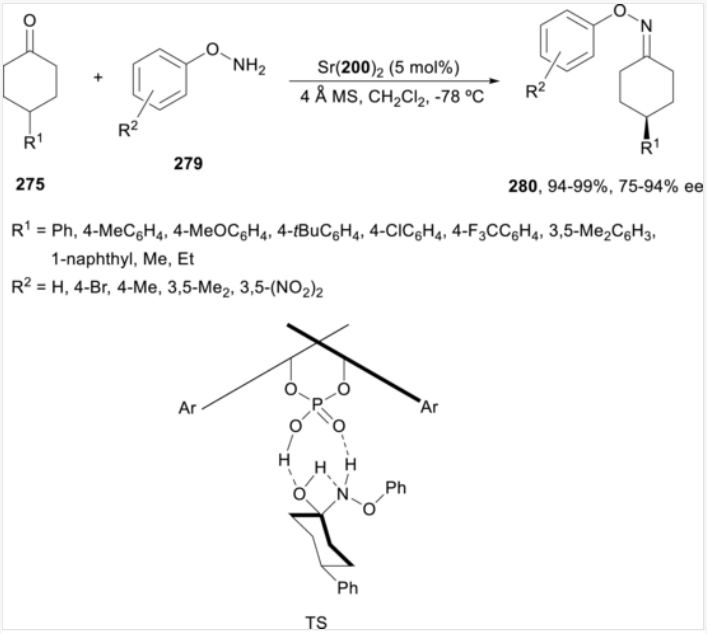


Pd/amine co-catalyzed desymmetrization of 4-substituted cycloalkanones **275** by an enantioselective hydroalkylation with butenamides **276**.

Antilla and co-workers [162] developed desymmetrization of 4-substituted cyclohexanones **275** by enantioselective formation of oxime ethers **280** (Scheme 88). The condensation with *O*-arylhydroxylamines **279** was catalyzed by a chiral BINOL-derived strontium phosphate prepared from CPA-**200**. Products **280** exhibit unique chirality because of the restricted rotation of the C═N bond. From the computed **TS** structures a favored **TS** was found.

alt-text: Scheme 88

Scheme 88

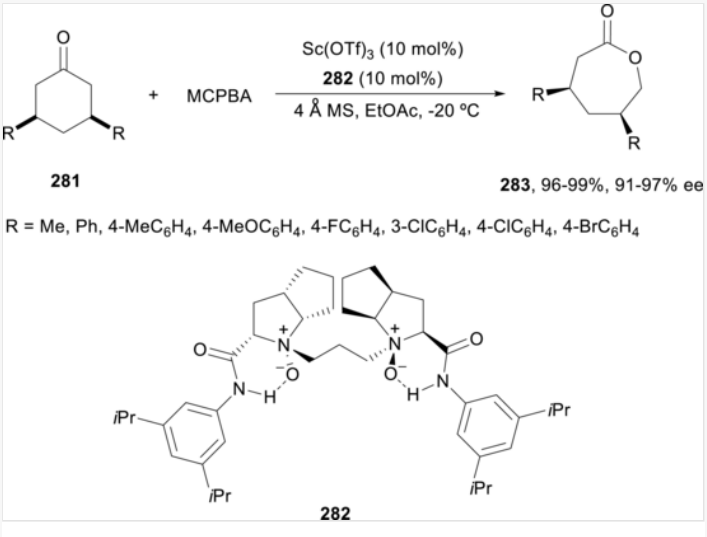


Sr-phosphate-catalyzed desymmetrization of 4-substituted cyclohexanones **275** by an enantioselective formation of oximes.

Asymmetric Baeyer-Villiger oxidation has been widely used for desymmetrization of 3-substituted cyclobutanones and 4-substituted cyclohexanones. Recently, *meso*-3,5-disubstituted cyclohexanones **281** have been desymmetrized using *N,N′*-dioxide **282** and $Sc(OTf)_3$ complex as catalyst (Scheme 89) [163]. Working with MCPBA as oxidant at −20 °C, the corresponding seven-membered lactones **283** were obtained in excellent yields and high enantioselectivities. The dimethyl substituted lactone was transformed into various natural products including mycolipenic acid, mycolipanolic acid and (−)-rasfonin. In addition, 3,4-diphenylcyclopentanone was transformed into the six-membered lactone in 99% yield and 96% ee.

alt-text: Scheme 89

Scheme 89



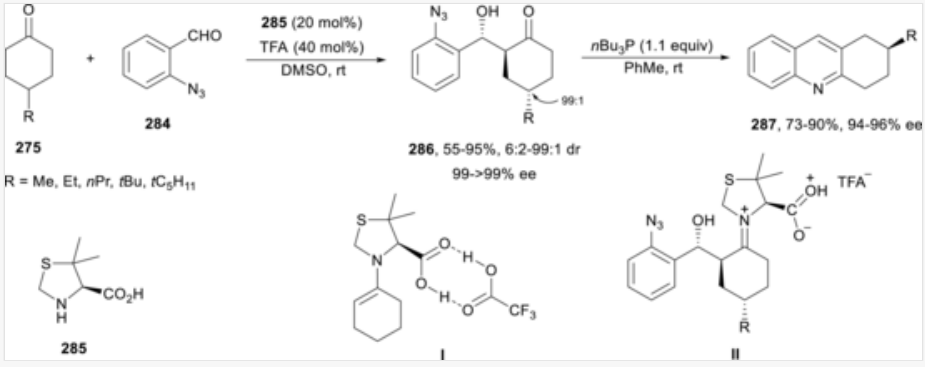
Sc(III)/*N,N′*-dioxide-catalyzed desymmetrization of 3,5-disubstituted cyclohexanones by an enantioselective Baeyer-Villiger oxidation.

4-Substituted cyclohexanones have been submitted to organocatalytic enantioselective desymmetrization by functionalization at the α-position through alkylation and aldol reactions, Michael additions, oxidations and asymmetric deprotonations [12]. These methods are mainly based on enamine organocatalysis using chiral amines.

Ramachary and Shruthi [164] used a combination of an amino acid **285** and trifluoroacetic acid as synergistic catalyst for the intermolecular aldol reaction of 4-substituted cyclohexanones **275** with 2-azidobenzaldehyde **284** (Scheme 90). The corresponding *anti*-aldols **286** were obtained in good yields and high diastereo- and enantioselectivities. Based on NMR studies it was explained that the mechanistic synergy of **285** and TFA, and the formation of enamine intermediate **I**, promotes the approach of the aldehyde from its *Re*-face giving the iminium intermediate **II**. Products **286** have been transformed into chiral tetrahydroacridines **287** by reaction with $n\mathrm{Bu}_3\mathrm{P}$ with slight decrease of enantioselectivity.

alt-text: Scheme 90

Scheme 90



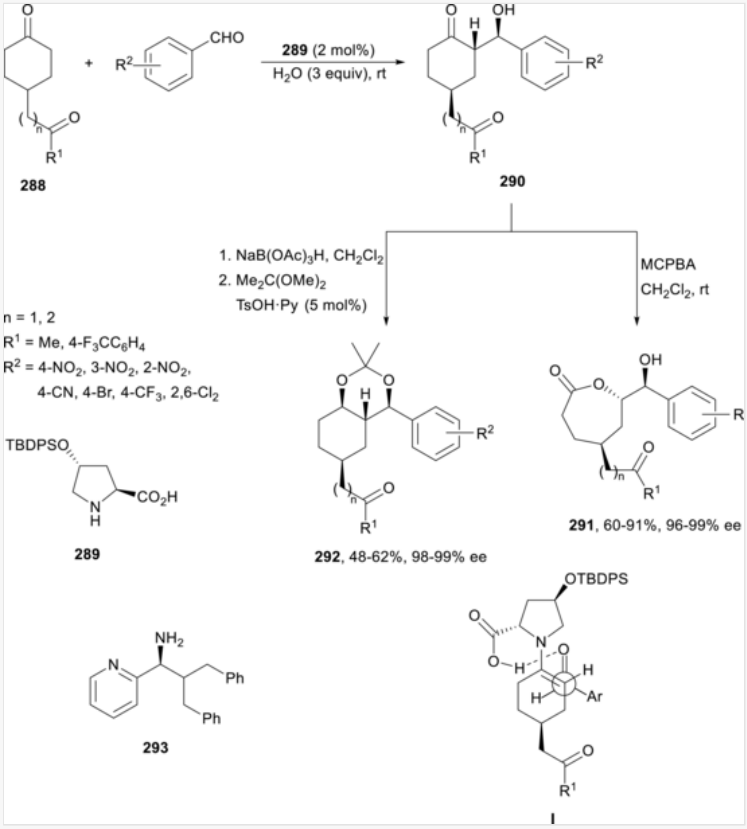
Organocatalyzed desymmetrization of 4-substituted cyclohexanones **275** by an enantioselective intermolecular aldol reaction.

4-Keto-substituted cyclohexanones **288** reacted with benzaldehydes regioselectively at the α-position of the cyclohexanone moiety giving the corresponding aldols **290** using TBDPSO-4-hydroxyproline **289** as organocatalyst (Scheme 91) [165]. Surprisingly, the methyl ketone remains unreacted and intramolecular ring closure was not observed. The resulting aldols **290** were stereochemically labile and were transformed into ketolactones **291** by treatment with MCPBA and into ketoacetonide products **292**. A model intermediate **I** was proposed to explain the *anti*-

diastereoselectivity (3.3:1->24; 1 dr) observed in the intermolecular aldol reaction. The same group achieved a switch in the stereogenic center at the 4-position of cyclohexanone when picolylamine **293** was used as organocatalyst [166].

alt-text: Scheme 91

Scheme 91

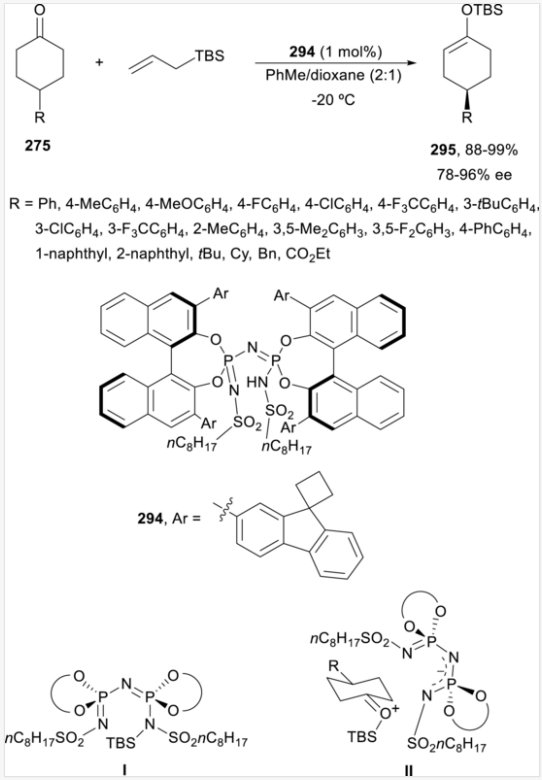


Organocatalyzed desymmetrization of 4-ketoalkyl-substituted cyclohexanones **288** by an enantioselective aldol reaction.

Recently, List and co-workers [167] reported an efficient desymmetrization of 4-substituted cyclohexanones **275** by enantioselective silyl enol ether formation. Using strongly acidic imidodiphosphorimidate **294** as catalyst and an allylsilane as silylating agent, enantioenriched enol silanes **295** were obtained in general with high yields and enantioselectivities (Scheme 92). These silicon-hydrogen exchange reaction enable access to enantiopure enol silanes *via* σ-bond metatheses. One example with 4-phenylcyclobutanone and a bicyclic cyclopentenone was also successfully desymmetrized. Several silyl enol ethers were transformed into different ketones with complete conservation of the enantiopurity. On the bases of NMR studies it was proposed that the initial silylation of the catalyst is the limiting step of the reaction giving the active silylated Lewis acid **I**. This intermediate **I** can activate the ketone by formation of the silyloxocarbenium ion pair **II**. Final deprotonation at the α-position of the silyloxocarbenium ion promotes the enantiopurity of the enol silane and regenerates the catalyst. Alternatively, a proto-desilylative kinetic resolution of racemic enol silanes with the carboxylic acid as silyl acceptor can be operating.

alt-text: Scheme 92

Scheme 92

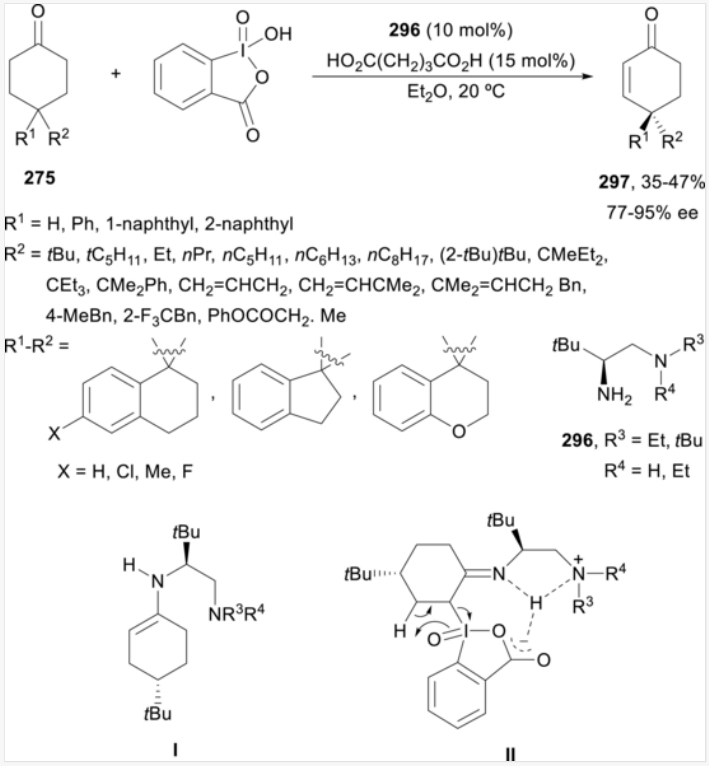


Organocatalyzed desymmetrization of 4-substituted cyclohexanones **275** by an enantioselective silyl enol ether formation.

Luo and co-workers [168] described a desymmetrization of 4-substituted cyclohexanones **275**, as well as 4,4-disubstituted ones, by dehydrogenation through enamine oxidation. The reaction was carried out using chiral primary amines **296** to form the corresponding enamines which were oxidized by 2-iodoxybenzoic acid (IBX) to produce 4-substituted cyclohexenones **297** in moderated yields and good enantioselectivities (Scheme 93). DFT calculations supported that the *S*-configured enamines **I** are slightly favored over the *R*-ones by 10 kK cal/mol. These enamines underwent α-oxidation with IBX to form intermediates **II**, which underwent a concerted β-H abstraction-elimination to afford the products. The enone moiety was submitted to conjugate addition, arylboronic acid addition, α-iodination, reductive radical cyclization and epoxidation to give the desired compounds as single diastereomers.

alt-text: Scheme 93

Scheme 93

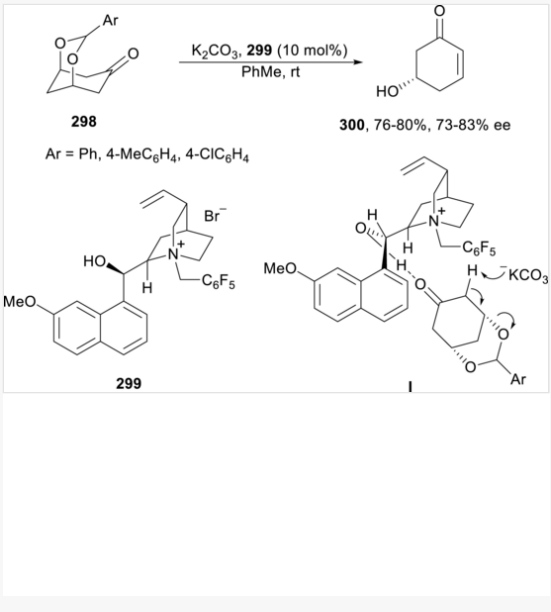


Organocalatyzed desymmetrization of 4-monosubstituted and 4,4-disubstituted cyclohexanones **275** by an enantioselective dehydrogenation.

Enantioselective desymmetrization of *cis*-2,5-*O*-arylidenecyclohexanones **298** has been performed under basic conditions using *Cinchona*-derived ammonium salts [169]. By using K_2CO_3 as base and the phase-transfer catalyst **299**, the corresponding enantioenriched (*S*)-5-hydroxycyclohex-2-enone (**300**) was obtained (Scheme 94). Transition state **I** has been proposed to explain the formation of the (*S*)-enantiomer. This compound **300** has been used as chiral building block for the synthesis of drugs and natural products.

alt-text: Scheme 94

Scheme 94

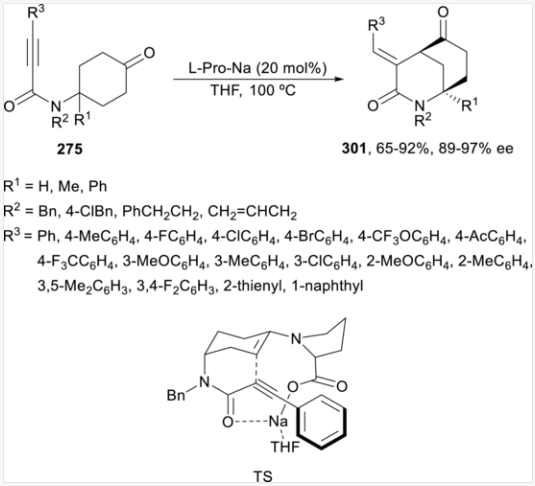


Phase-transfer catalyzed desymmetrization of cyclohexanones **298** by an enantioselective β-elimination.

Intramolecular nucleophilic α-addition to 4,4-disubstituted cyclohexanones **275** bearing a propiolamide unit took place through a 6-*exo*-*dig*-cyclization using sodium L-prolinate to provide bicyclic products **301** (Scheme 95) [170]. This enantioselective desymmetrization involves the formation of the proline-derived **TS** being the most stable according to DFT calculations. This is consistent with the high enantioselectivity observed. One of these products bearing a morphan scaffold was transformed into a precursor of the immunosuppressant FR901483.

alt-text: Scheme 95

Scheme 95

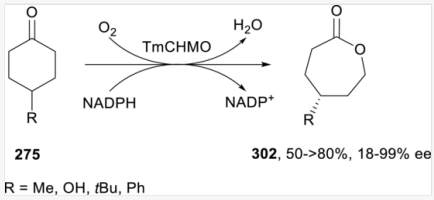


Organocatalyzed desymmetrization of cyclohexanones **275** by an enantioselective intramolecular cyclization.

Enzymatic Baeyer-Villiger oxidation has been applied to the desymmetrization of 4-substituted cyclohexanones **275** and also of *cis*-3,5-dimethylcyclohexanone (**281**) and 4-substituted cyclobutanones [171]. Thermostable Baeyer-Villiger monooxygenase TmCHMO from *Thermocrispum municipale* gave the corresponding seven-membered (*S*)-lactones **302** in high yields and enantioselectivities (Scheme 96). In the case of **281** the corresponding lactone **283** (R = Me) was obtained with (4*S*,6*R*)-configuration in 99% ee. Reversal of enantioselectivity was achieved by evolution based on iterative saturation mutagenesis.

alt-text: Scheme 96

Scheme 96



Enzymatic desymmetrization of 4-substituted cyclohexanones **275** by an enantioselective Baeyer-Villiger oxidation.

5.2 Cyclohexadienones

Desymmetrization of cyclohexadienones has received considerable attention especially in the last 20 years. Inter and intramolecular asymmetric reactions are the main strategies using transition metals or organocatalysis (Fig. 3). These highly functionalized molecules became very useful building blocks for the synthesis of natural products. They are

easily accessible mainly by oxidative dearomatization of phenols mainly by hypervalent iodine reagents. Several excellent reviews have covered this subject in the last recent years either partially [13,14,21] or specifically [7,8,172–174].

Images are optimised for fast web viewing. Click on the image to view the original version.

alt-text: Fig. 3

Fig. 3

Inter and intramolecular desymmetrization of cyclohexadienones.

5.3 1,3-Diketones

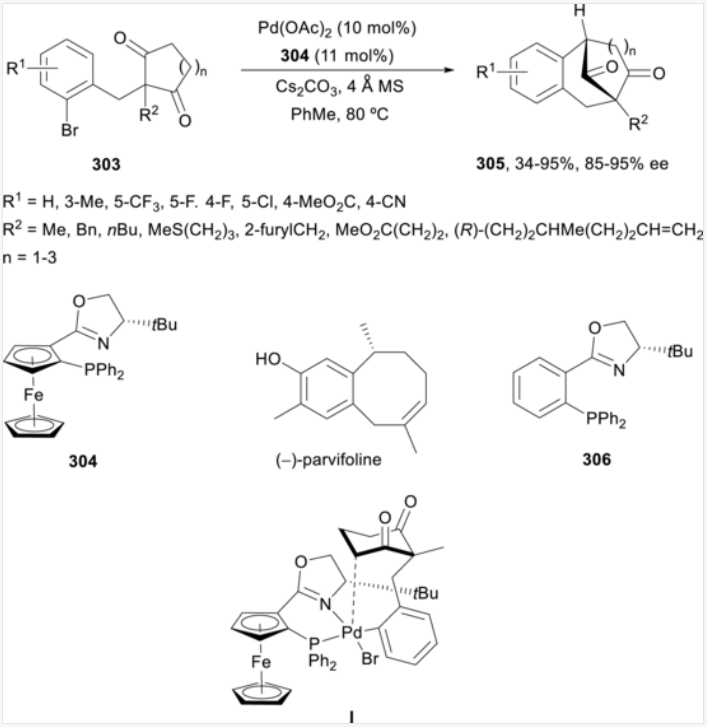
Desymmetrization of acyclic and cyclic 1,3-diketones is a fundamental methodology based on modification of one of the two carbonyl groups mainly based on aldol-type and reduction reactions [6,8,13,14,17,25,175,176].

Intramolecular desymmetric α-arylation of cycloalkane-1,3-diones **303** has been achieved using a Pd catalyst and Foxap **304** as a chiral ligand (Scheme 97) [177]. In this case, the α-arylation occurred at the α-position of the carbonyl group to build bicyclic diketones **305** with high enantioselectivities. This methodology has been used as the key step in the formal synthesis of (−)-parvifoline, a sesquiterpene isolated from the species *Coreopsis*, using *ent*-**304** as ligand. The observed stereochemistry was explained by model **I** in which after oxidative addition of Pd(0) to the aryl bromide, this aryl group coordinated to Pd is *trans* to the PPh_2 group in the ligand. The diketone occupies the opposite side of the bulky *t*-Bu group on the ligand. Bicyclo[3.3.1]nonanones **305** (n = 2) have been prepared starting from cyclohexa-1,3-diones **303** (n = 2) using *t*BuPhox (**306**) as a chiral ligand in moderate to good yields (44–84%) and enantioselectivities (63–86%) [178].

Images are optimised for fast web viewing. Click on the image to view the original version.

alt-text: Scheme 97

Scheme 97



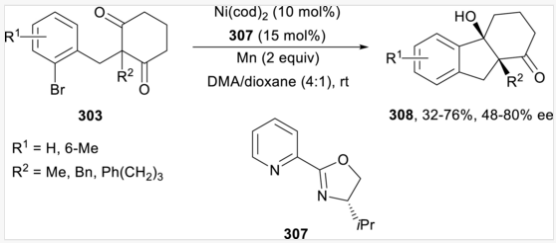
Pd-Catalyzed desymmetrization of cycloalkane-1,3-diones **303** by an enantioselective intramolecular α-arylation.

Cyclohexa-1,3-diones **303** underwent intramolecular addition of aryl bromide to the carbonyl group affording bicyclic ketones **308** (Scheme 98) [179]. In this process using $Ni(cod)_2$, Mn as reductant and the oxazoline chiral ligand **307** products **308** were obtained in moderate enantioselectivity.

Images are optimised for fast web viewing. Click on the image to view the original version.

alt-text: Scheme 98

Scheme 98



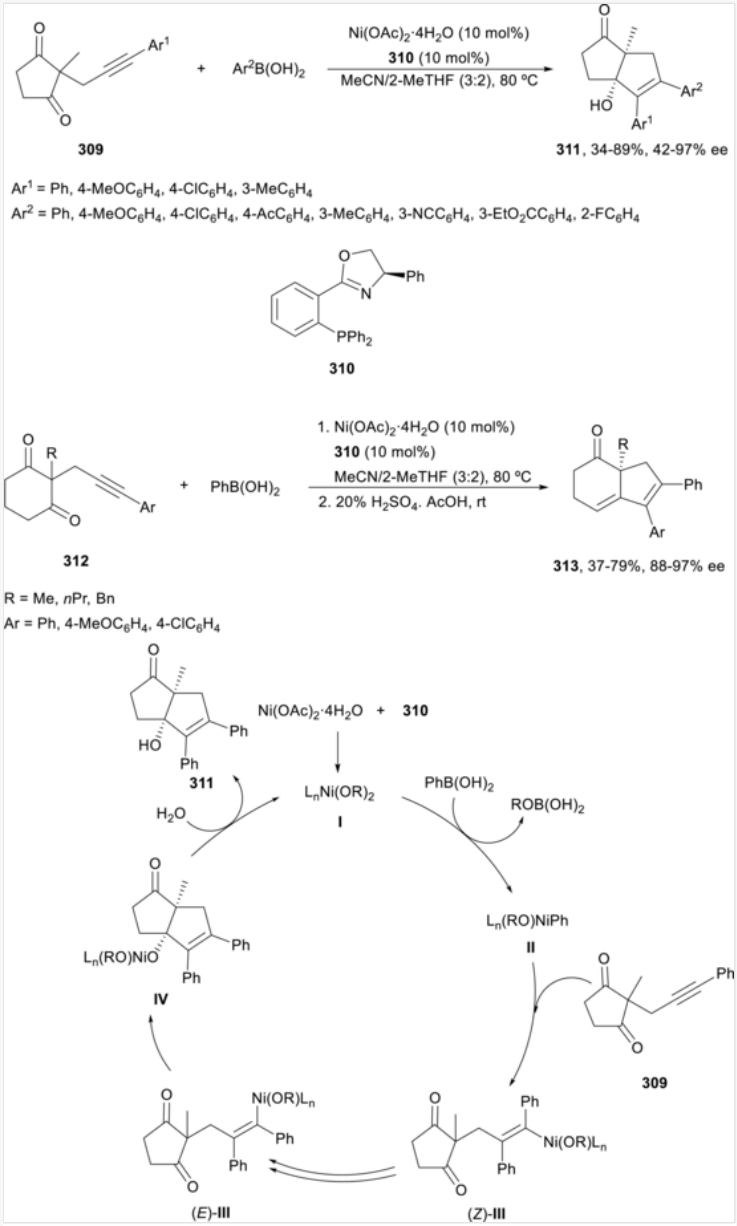
Ni-Catalyzed desymmetrization of cyclohexane-1,3-diones **303** by an enantioselective intramolecular addition.

Nickel-catalyzed addition of arylboronic acids to the alkynyl group of 2-substituted cyclopentane-1,3-diones **309** has been described by Lam and co-workers [180]. Using (*R*)-PhPhox **310** as a chiral ligand in a mixture 3:2 of acetonitrile and Me-THF at 80 °C intramolecular addition to the carbonyl group provided bicyclic ketones **311** (Scheme 99). In the proposed catalytic cycle for cyclopentane-1,3-dione as a representative example, initial transmetalation of phenylboronic acid with the Ni complex **I** gave species **II**. *syn*-Arylnickelation of **309** with **II** gave after reversible *E/Z* isomerization the alkenylnickel intermediate (*E*)-**III**. Cyclization of (*E*)-**III** provided the nickel alkoxide **IV**, which by protonolysis released product **311**. In the case of cyclohexane-1,3-diones **312** partial dehydration of the intermediate hydroxyketones took place to afford bicyclic dienes **313**. After treatment of the crude mixtures with 20% H_2SO_4 in AcOH products **313** were obtained in good yields and enantioselectivities.

Images are optimised for fast web viewing. Click on the image to view the original version.

alt-text: Scheme 99

Scheme 99



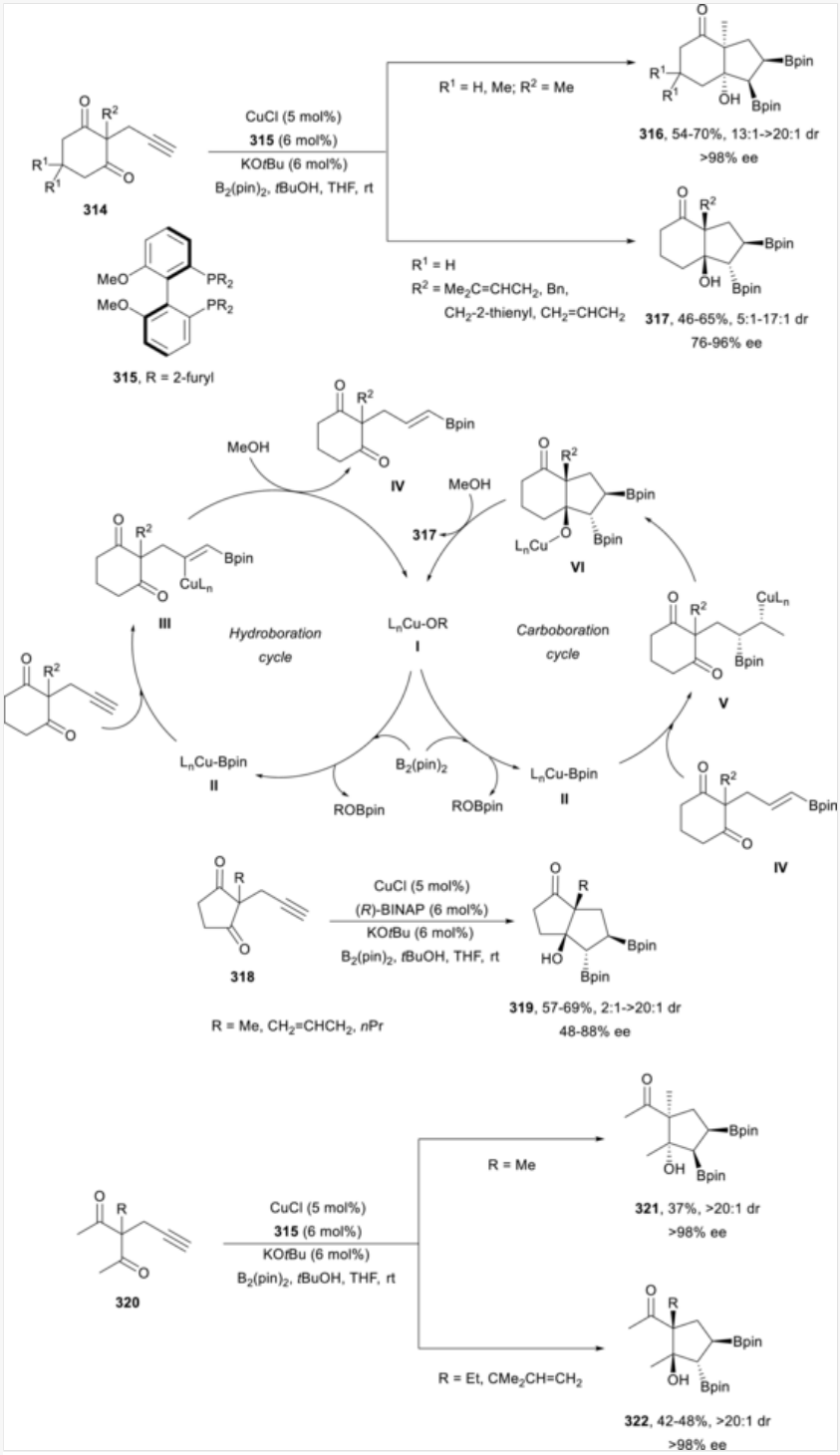
Ni-Catalyzed desymmetrization of 2-alkenyl cycloalkane1,3-diones **309** and **312** by an enantioselective tandem reaction with arylboronic acids and subsequent intramolecular cyclization.

Acyclic and cyclic 1,3-diketones bearing an alkyne substituent at the 2-position undergoes desymmetrization by copper-catalyzed tandem hydroboration/borylative cyclization [181]. In the case of cyclohexane-1,3-diones **314** and diphosphine **315** as a chiral ligand, the reaction with B_2pin_2/*t*BuOH afforded bis-borylhydrindanes **316** or **317** with

moderate yields and high diastereo and enantioselectivities (Scheme 100). Dual catalytic cycles have been proposed starting from L_nCu-OR (**I**) as catalyst, transmetalation with B_2pin_2 generates the L_nCu-Bpin complex **II**. Regioselective *syn* migratory insertion across alkyne **314** afforded the alkenyl copper **III**, which by protonation by MeOH gave *trans*-β-vinylboronic ester **IV**. In the carboboration cycle, migratory insertion of **II** across vinylboronic ester **IV** gave intermediate **V**, which cyclized to **VI**. Final protonation of the Cu–O bond of intermediate **VI** furnished product **317**. In the case of cyclopentane-1,3-diones **318** and using (*R*)-BINAP as a chiral ligand [5,5]-fused carbocycles **319** were obtained, whereas acyclic 1,3-diketones **320** provided with ligand **315** products **321** (R = Me) or **322** (R ≠ Me). It means that depending on the substrate and on the ligand stereoinvertive and stereoretentive cyclization pathways were observed.

alt-text: Scheme 100

Scheme 100

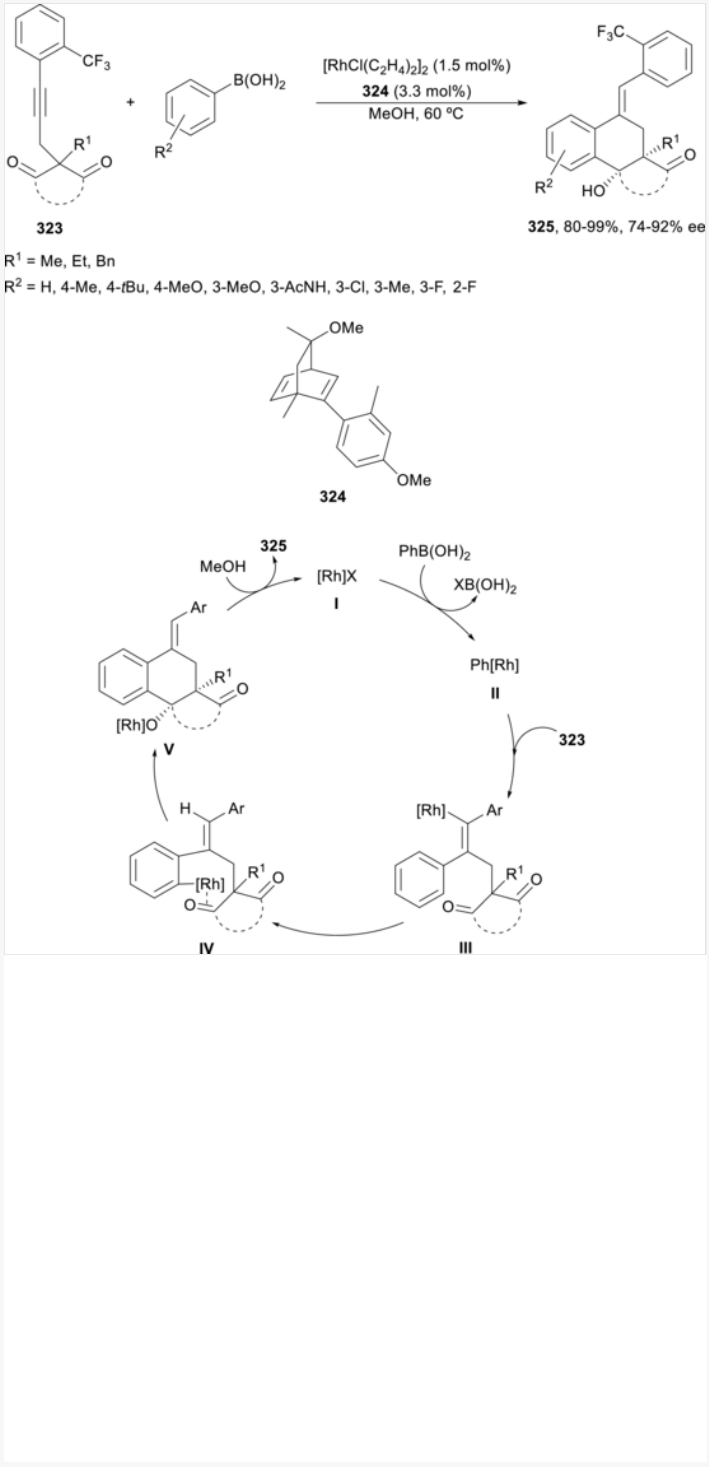

CuCl (5 mol%)
315 (6 mol%)
KOtBu (6 mol%)
B2(pin)2, tBuOH, THF, rt
314
R1 = H, Me; R2 = Me
316, 54-70%, 13:1->20:1 dr
>98% ee
R1 = H
R2 = Me2C=CHCH2, Bn,
CH2-2-thienyl, CH2=CHCH2
317, 46-65%, 5:1-17:1 dr
76-96% ee
315, R = 2-furyl
MeOH
IV
317
VI
III
Hydroboration
cycle
LnCu-OR
I
Carboboration
cycle
V
LnCu-Bpin
II
B2(pin)2
ROBpin
318
R = Me, CH2=CHCH2, nPr
CuCl (5 mol%)
(R)-BINAP (6 mol%)
KOtBu (6 mol%)
B2(pin)2, tBuOH, THF, rt
319, 57-69%, 2:1->20:1 dr
48-88% ee
320
R = Me
321, 37%, >20:1 dr
>98% ee
R = Et, CMe2CH=CH2
322, 42-48%, >20:1 dr
>98% ee

Cu-Catalyzed desymmetrization of 1,3-diketones **314**, **318** and **320** by an enantioselective hydroboration/borylative cyclization.

1-Tetraols **325** bearing two contiguous quaternary carbon centers have been prepared by reaction of 2-alkynyl-1,3-diketones **323** with arylboronic acids under Rh catalysis (Scheme 101) [182]. This asymmetric desymmetrization was carried out using diene **324** as a chiral ligand and as substrates cyclohexane-1,3-diones, cyclopentane-1,3-diones and pentane-2,4-dione giving products **325** in >99% diastereoselectivity. In the proposed catalytic cycle, a hydroxorhodium(I) catalytic species **I** underwent transmetalation with the arylboronic acid to give the arylrhodium intermediate **II**. Then, a regioselective insertion into the alkyne moiety gave a vinylrhodium species **III**, which after 1,4-shift generates a new arylrhodium species **IV**. This intermediate **IV** is trapped by the ketone through an intramolecular 1,2-addition to provide the alkoxorhodium intermediate **V**, which after protonation afforded the 1-tetraol.

alt-text: Scheme 101

Scheme 101

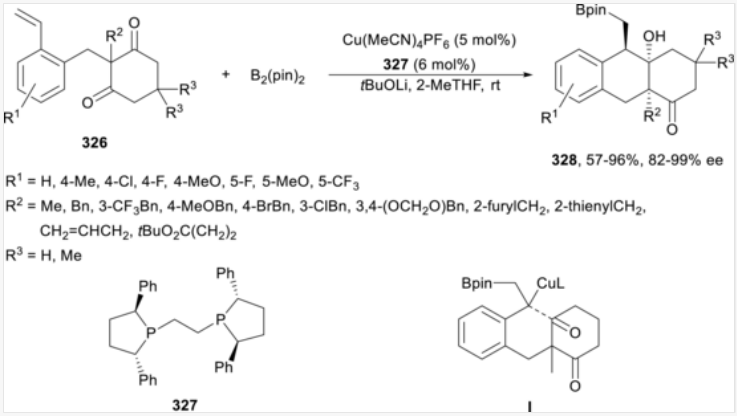


Rh-Catalyzed desymmetrization of 2-alkynyl-1,3-diketones by an enantioselective arylative cyclization.

A desymmetrization of 2-(2-vinylbenzyl)-1,3-diketones **326** is based on the borylative coupling of styrenes and ketones [183] The reaction involves an initial enantioselective borylcupration of the styryl unit followed by 1,2-addition to the carbonyl group to form chiral bicyclic compounds **328** (Scheme 102). This copper-catalyzed reaction was performed using diphosphine (*S*)-Ph-BPE (**327**) as a chiral ligand and mainly with cyclohexane-1,3-diones by intermediacy of benzylcopper **I**.

alt-text: Scheme 102

Scheme 102



Cu-Catalyzed desymmetrization of 2-styrylmethyl-1,3-cyclohexanones by an enantioselective borylative coupling.

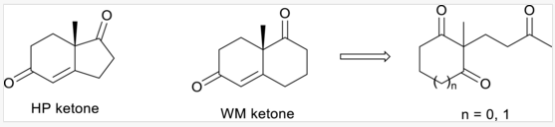
Reductive desymmetrization of 2,2-disubstituted-1,3-diketones to β-hydroxy ketones under metal catalysis has been mainly performed by Corey-Bakshi-Shibata monoreduction with catecolborane using a chiral oxazaborylidine as catalyst and by an asymmetric transfer hydrogenation catalyzed by Ru, Ir and Pd complexes. This particular desymmetrization has been recently covered by Yu, Zhou and co-workers [175].

Organocatalyzed desymmetrization has been widely performed by intramolecular aldol-type reactions mainly by the so-called Hajos-Parrish-Eder-Sauer-Wiechert (HPESW) reaction [12,13,176,184] using Michael adducts of 2-substituted 1,3-diketones to α,β-unsaturated ketones. It allows the facile synthesis of enantioenriched Hayos-Parrish (HP) and Wieland-Miescher (WM) ketones and their derivatives, which are very useful building blocks for numerous natural products (Fig. 4). Recent developments in this area follows.

Images are optimised for fast web viewing. Click on the image to view the original version.

alt-text: Fig. 4

Fig. 4



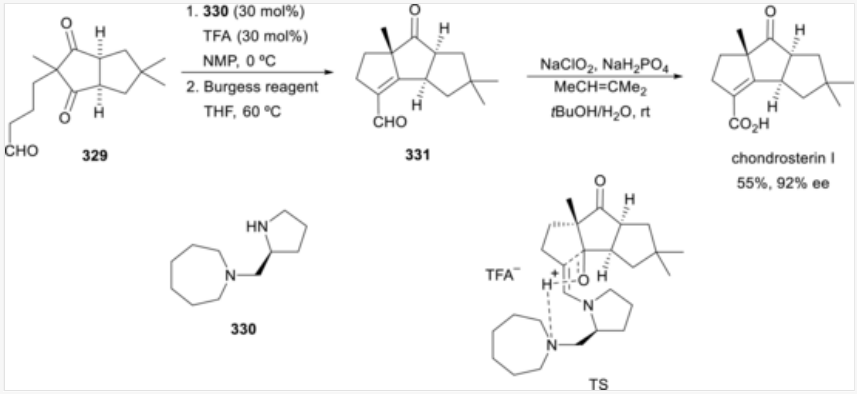
Hayos-Parrish and Wieland-Miescher ketones.

Recently, Ito and co-workers [185] reported the total synthesis of chondrosterins I and J produced by the marine fungus *Chondrostereum* sp., isolated form the coral *Sarcophyton tortuosum*. The synthesis is based on an organocatalyzed intramolecular aldol reaction of compound **329** with diamine **330** and trifluoroacetic acid as catalysts (Scheme 103). This process afforded chondrosterin I in 55% yield and 92% ee resulting from oxidation of the aldol derivative **331**. **TS** has been proposed to explain the stereoselectivity of the aldol reaction.

Images are optimised for fast web viewing. Click on the image to view the original version.

alt-text: Scheme 103

Scheme 103

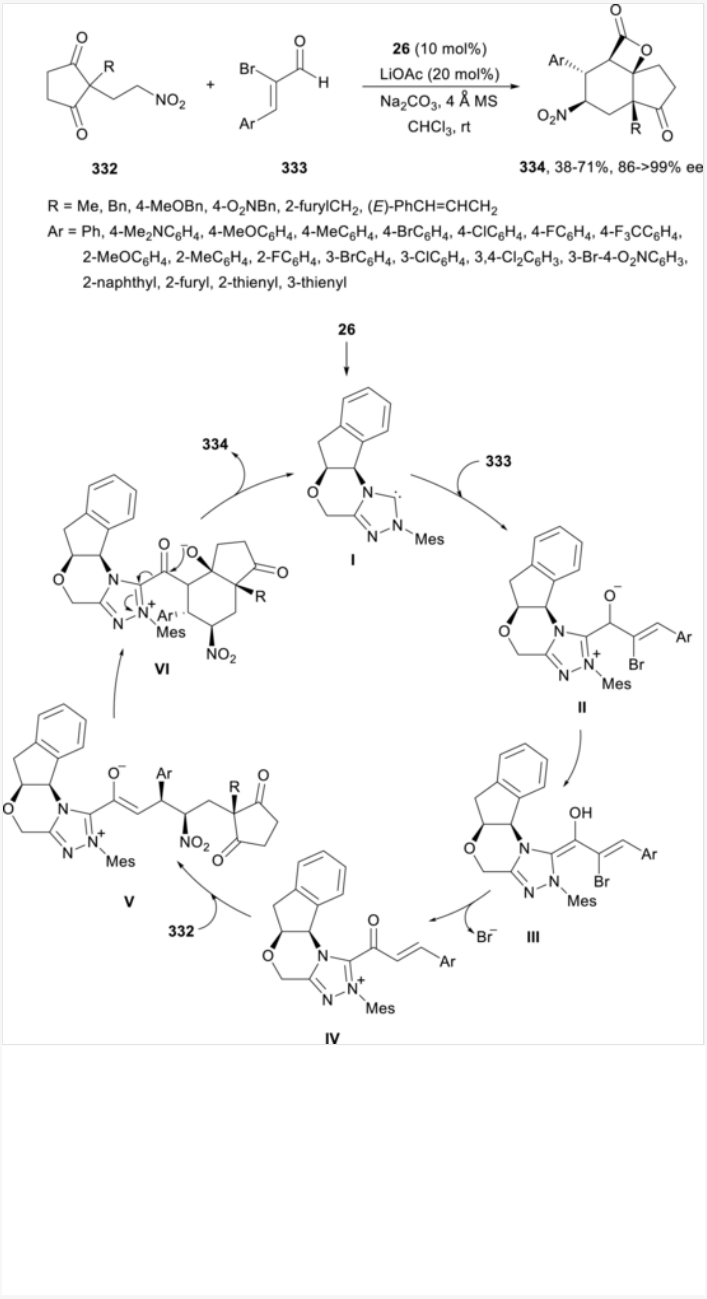


Organocatalyzed desymmetrization of 1,3-diketone **329** by an enantioselective intramolecular aldol reaction. Synthesis of chondrosterin I.

The NHC-catalyzed desymmetrization of cyclic 1,3-diketones has been recently performed by Biju and co-workers [186]. By an intramolecular reaction of 1,3-diketones **332** with 2-bromoenals **333** and the chiral triazolium salt **26** resulted tricyclic β-lactones **334** in moderate yields, high enantioselectivities and >20:1 dr in all cases (Scheme 104). In the proposed catalytic cycle the NHC carbene **I**, resulting from the triazolium salt **26**, generates the α,β-unsaturated acylazolium intermediate **II**, which after proton transfer forms the Breslow intermediate **III**. The key α,β-unsaturated acylazolium **IV** was formed by debromination of **III**, which underwent Michael addition of the diketone from the *Si*-face leading to the enolate intermediate **V**. Subsequent intramolecular aldol reaction provided the alkoxide intermediate **VI** followed by intramolecular nucleophilic acylation giving products **334**.

alt-text: Scheme 104

Scheme 104

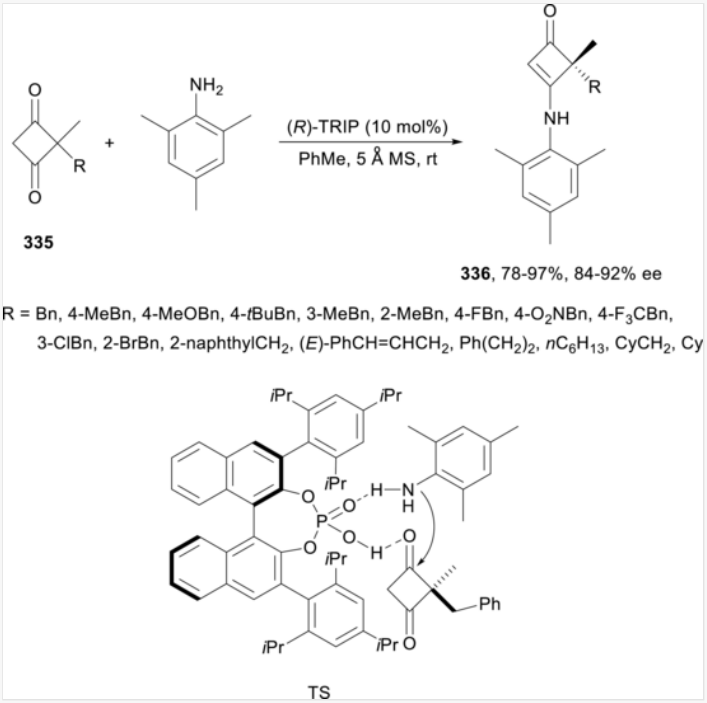


NHC-catalyzed desymmetrization of 1,3-diketones **332** by an enantioselective reaction with 2-bromoenales **333**.

Recent work on enantioselective desymmetrization of cyclobutane-1,3-diones **335** by carbonyl-amine condensation has been described using phosphoric acid (*R*)-TRIP (**200**) as chiral catalyst [187]. By reaction of diones **335** with 2,4,6-trimethylaniline at room temperature the corresponding β-aminoenaminones **336** were obtained in very good yields and up to 92% ee (Scheme 105). According to control experiments it has been proposed that the hydroxy group in the phosphoric acid formed a hydrogen bond with one of the carbonyl groups of the cyclobutane-1,3-dione and the P═O group also formed a hydrogen bonding interaction with the amino group as represented in **TS**.

alt-text: Scheme 105

Scheme 105

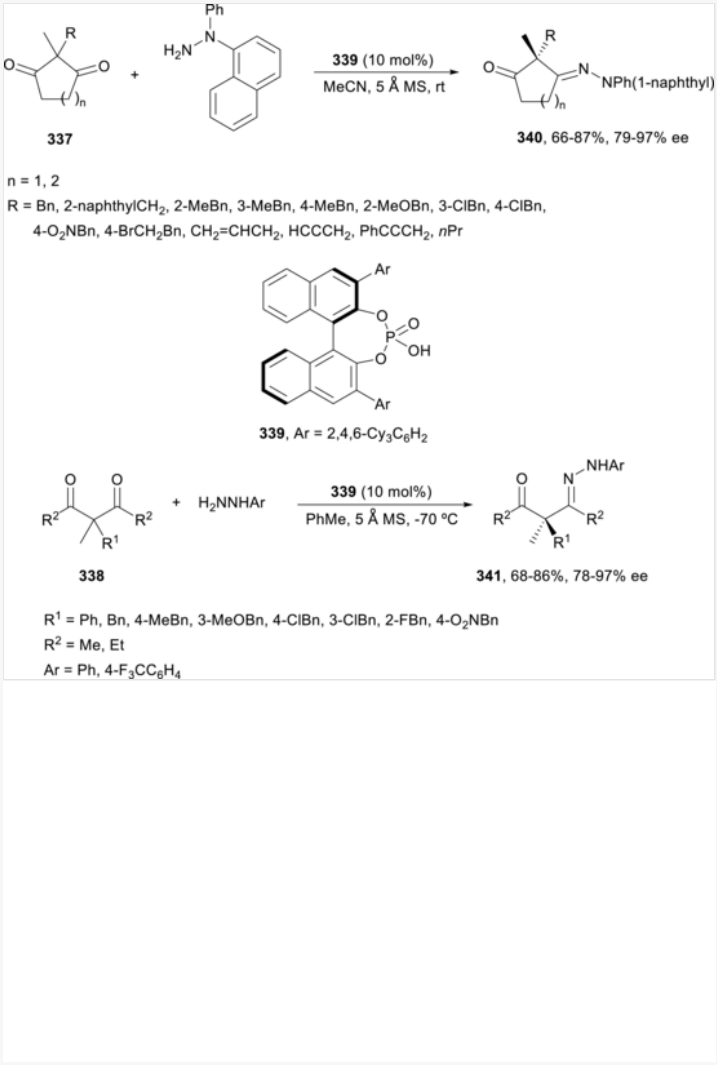


Phosphoric acid-catalyzed desymmetrization of cyclobutane-1,3-diones **335** by an enantioselective condensation with 2,4,6-trimethylaniline.

A general desymmetrization of acyclic and cyclic 1,3-diones has been carried out by simple condensation with hydrazines using chiral phosphoric acid **339** as catalyst [188]. Cyclopentane- and cyclohexane-1,3-diones **337** reacted with *N*-phenyl-*N*-(1-naphthyl)hydrazine to give hydrazones **340**, whereas acyclic 1,3-diones **338** reacted with monosubstituted hydrazines to provide hydrazones **341** in good yields and enantioselectivities (Scheme 106). According to DFT calculations **TS**-*R* is 1.3 kcal/mol lower in energy than the other **TS**-*S* leading to (*S*)-products.

alt-text: Scheme 106

Scheme 106

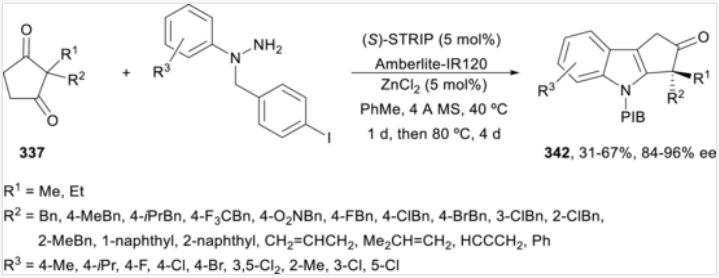


Phosphoric acid-catalyzed desymmetrization of cyclic **337** and acyclic **338** 1,3-diones by an enantioselective condensation with hydrazines.

Fisher indolization of 4-substituted cyclohexanones using chiral phosphoric acid as catalyst was initially described by List and co-workers in 2011 [189]. Recently, Jindal, Mukherjee and co-workers [190] applied this methodology to the enantioselective desymmetrization of cyclopentane-1,3-diones **337** (n = 1) using *p*-iodobenzyl (PIB)-protected phenylhydrazines (Scheme 107). This reaction was carried out using (*S*)-STRIP (**173**) and $ZnCl_2$ as catalysts (Lewis acid assisted Brønsted acid) affording cyclopenta[*b*]indole derivatives **342** with good to excellent enantioselectivities proceeding through dynamic kinetic resolution (DKR) of the initially formed enantiomeric hydrazones. DFT calculations focused on the [3,3]-sigmatropic rearrangement step showed lower distortion in the **TS**-*R* than **TS**-*S* with a difference of 2.0 kcal/mol.

alt-text: Scheme 107

Scheme 107



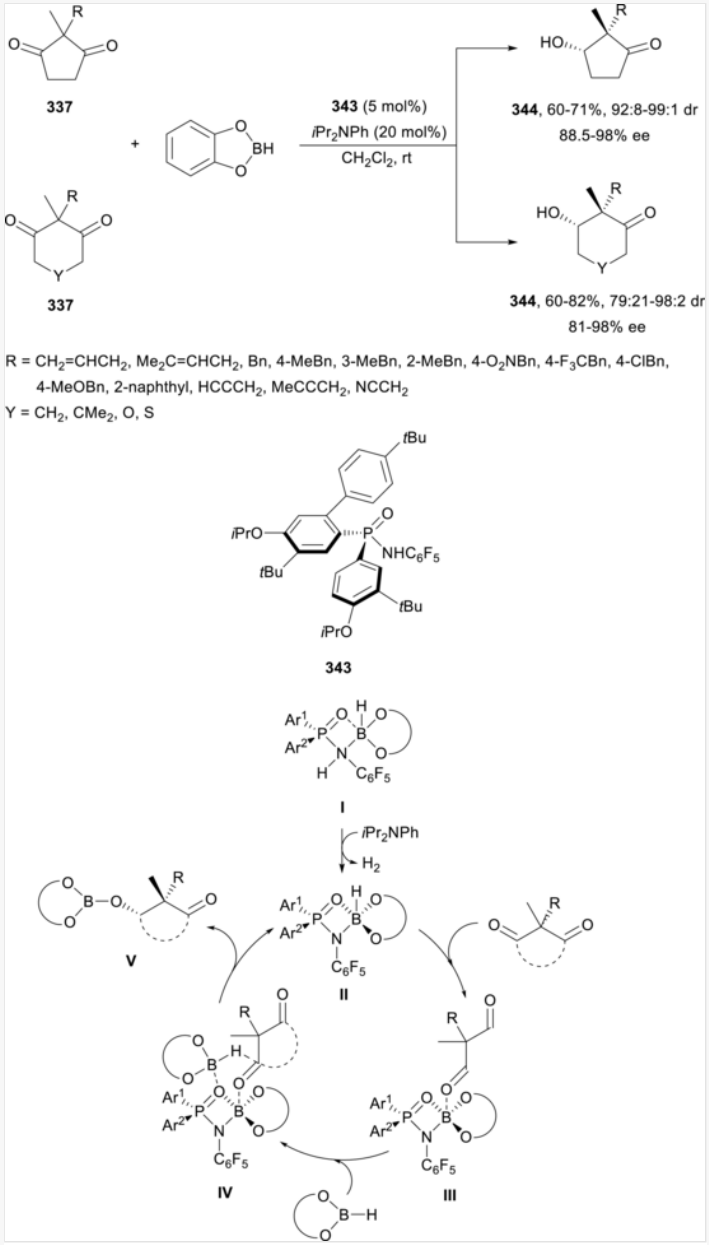
Phosphoric acid/$ZnCl_2$ co-catalyzed desymmetrization of cyclopentane-1,3-diones **337** by an enantioselective Fischer indolization.

General methods for the monoreduction of cyclic α,α-disubstituted 1,3-diketones **337** to the corresponding β-hydroxy ketones include transition-metal-catalyzed hydrogenations or transfer hydrogenations, oxazaborolidine-catalyzed reductions and enzymatic processes.

Recent advances involved the use of catecholborane as reductant and a chiral phosphinamide **343** as new organocatalyst for the general reduction of 1,3-diones **337** (Scheme 108) [191]. Enantioenriched five and six-membered 3-hydroxy ketones **344** were obtained with high enantio- and diastereoselectivity and the catalyst could be recovered in >90% yield by column chromatography and reused. On the basis of NMR experiments it was proposed a plausible catalytic cycle in which the boraphosphinimidate **II** is formed by extrusion of H_2 in complex **I** under the assistance of the base iPr$_2$NPh. Intermediate **II** acted as a bifunctional catalytic species coordinating the 1,3-diones to form the sterically favored intermediate **III**. After coordination of **III** with the Lewis acid catecholborane complex **IV** was formed. Finally, hydride transfer to the dione regenerated **II** and delivered borate **V**.

alt-text: Scheme 108

Scheme 108



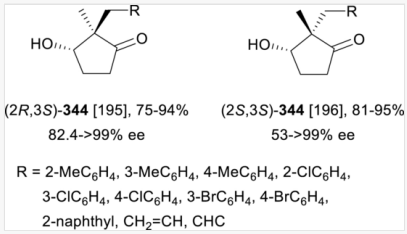
Phosphinamide-catalyzed desymmetrization of cyclic 1,3-diones by an enantioselective reduction with catecholborane.

Biocatalyzed reduction of cyclic 1,3-dienes [25,192] has been mainly carried out with the yeast *Sccharomices cerevisae*. Recently the β-hydroxycyclopentenone *ent*-**344** (R = allyl) has been employed as chiral building block for the total synthesis of diterpenoids (−)-hamigeran B, (−)-4-bromohamigeran B [193] and **344** (R = allyl), for cyrneines A and B, glaucopine C and (+)-allocyatin [194]. Chen, Wu, Zhu and co-workers described the reduction of 2,2-

disubstituted-1,3-cyclopentanediones by carbonyl reductase RasADH obtained through structure-guided direct evolution from *Ralstonia* sp. to give (2*R*,3*S*)-ketols **344** (Fig. 5) [195]. The same group obtained through the same strategy an engineered carbonyl reductase (M4) from *Sporobolomyces salmonicolor* AKU4429, which afforded (2*S*,3*S*)-stereoisomers **344** in >98% ratio (Fig. 5) [196].

alt-text: Fig. 5

Fig. 5

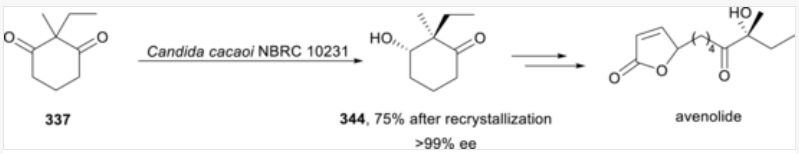


Reduction of 2,2-disubstituted-1,3-cyclopentanediones **337** with mutant carbonyl reductases.

(2*R*,3*S*)-2-Ethyl-2-methyl-3-hydroxycyclohexanone (**344**) has been used for the synthesis of the microbial hormone avenolide, which is produced by *Streptomicyn avermitilis*, by Monna and Fuhshuku [197]. *Candida cacaoi* NBRC 10231 and *Pichia farinose* NBCR 10896, two types of yeast species, reduced 2-ethyl-2-methylcyclohexane-1,3-dione preferentially to the desired (2*R*,3*S*)-diastereomer, whereas the bacterial sp *Marganella morganti* NBRC 3168, *Providencia rettgeri* NBRC 13501 and *Escherichia fergusonii* NBRC 102419 produced mainly the (2*S*,3*S*)-diastereomer (Scheme 109).

alt-text: Scheme 109

Scheme 109



Biocatalyzed desymmetrization of 2-ethyl-2-methylcyclohexane-1,3-dione by *Candida cacaoi* NBRC 10231 reduction.

5.4 Cyclopentene-1,3-diones

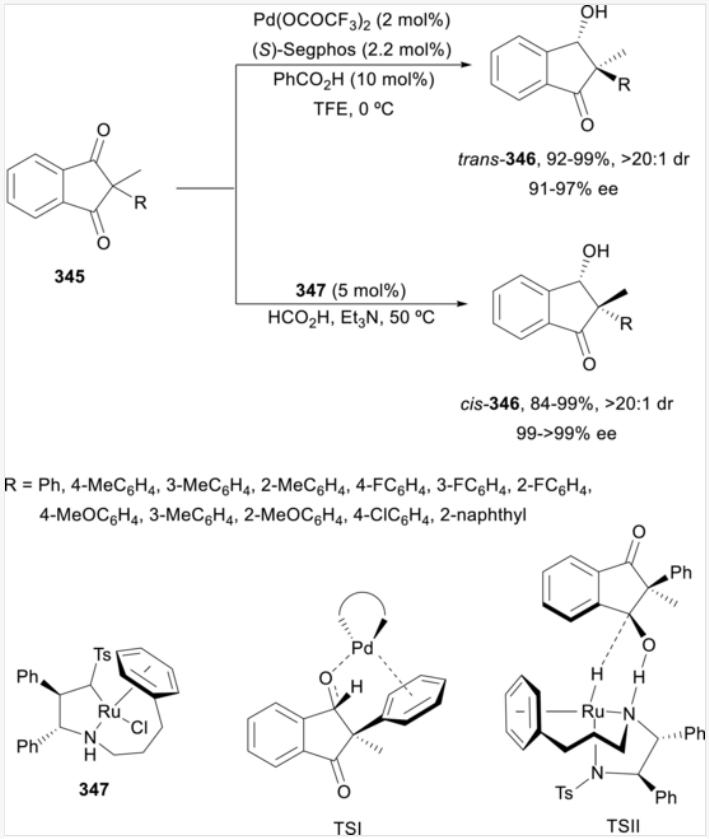
Desymmetrization of cyclopentane-1,3-diones *via* asymmetric metal-catalyzed and organocatalyzed Michael addition and cycloaddition reactions has been recently covered by Das [198].

A recent NHC-catalyzed desymmetrization of cyclic 1,3-diketones (Scheme 104) [186] has been applied also to cyclopentane-1,3-diones. Pd-catalyzed hydrogenative desymmetrization of 1,3-indanediones **345** allowed the preparation of *trans*-β-hydroxy ketones **346** with high enantio- and diastereoselectivity [199]. The process was carried out using (*S*)-Segphos as a chiral ligand in trifluoroethanol under 300 psi H_2 pressure in the presence of benzoic acid (Scheme 110). According to mechanistic studies and DFT calculations the observed diastereoselectivity resulted from

the charge-charge interaction between the Pd and the aromatic ring of the diketone as shown in **TSI**. However, the Ru-catalytic transfer hydrogenative desymmetrization afforded the *cis*-isomer **346** using catalyst **347** (Scheme 107). Due to steric hindrance **TSII** has been proposed to be the most favored explaining the resulting stereoselectivity. These methodologies have been applied to cyclopentane-1,3-diones and cyclic 1,3-diones.

alt-text: Scheme 110

Scheme 110



Pd and Ru-Catalyzed desymmetrization of 1,3-indanediones **345** by an enantioselective reduction.

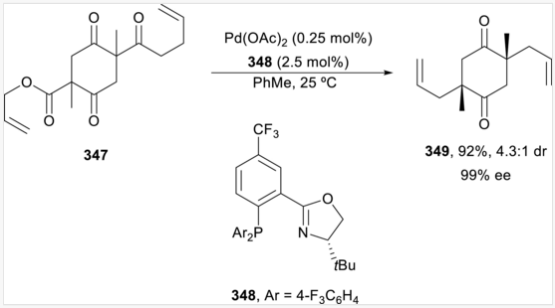
5.5 Other diketones

Cyclic 1,4-diketone **347** has been used as starting material for the total synthesis of (−)-cyanthiwigin E, isolated from the marine sponge *Myrme kioderma styx*, with interesting biological activity toward primary tumor cells, by Enquist and Stoltz [201]. When this 1,4-diketone was submitted to a double catalytic enantioselective decarboxylative

allylation, diluted reaction conditions must be used. In 2016 the same group [202] improved this key desymmetrization step using $Pd(OAc)_2$ and (*S*)-CF_3-*t*BuPhox ligand **348** with lower catalyst loading and 10 times less solvent giving the desired diketone (*R*,*R*)-**349** in good dr and excellent ee (Scheme 111).

alt-text: Scheme 111

Scheme 111

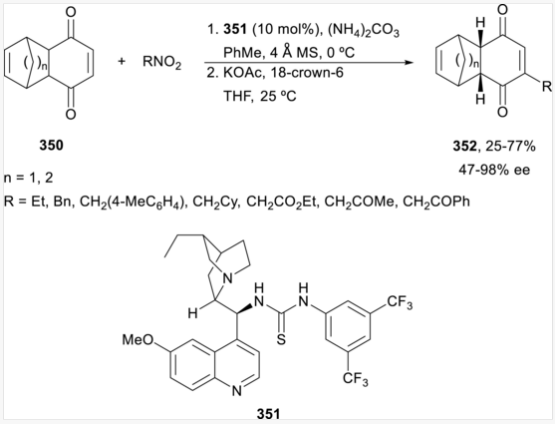


Pd-Catalyzed desymmetrization of 1,4-diketone **347** by an enantioselective decarboxylative allylation.

Norbornenequinones **350** (n = 1), resulting from the Diels-Alder reaction of cyclopentadiene and *p*-benzoquinone, have been widely used as building blocks for the synthesis of several quinonoid natural products by Mehta's group. Srakar and Mukherjee [203] reported the desymmetrization of different compounds **350** by an organocatalyzed Csp^2–H alkylation with nitroalkanes [204]. Chiral thiourea **351** was used as bifunctional catalyst affording selected products **352** (Scheme 112). The reaction took place by initial conjugate addition of nitroalkanes to give intermediate **I**, which is the enantiodetermining step of the reaction, followed by HNO_2 elimination to intermediate **II** and final isomerization.

alt-text: Scheme 112

Scheme 112



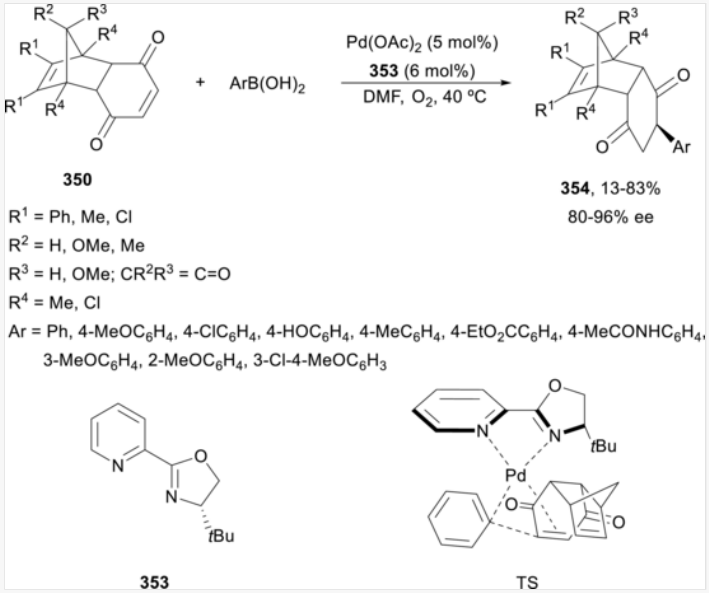
Organocatalyzed desymmetrization of norbornenoquinones **350** by an enantioselective Csp^2–H alkylation with nitroalkanes.

Lee and co-workers [205] reported the desymmetrization of norbornenequinones **350** (n = 1) by a Pd-catalyzed conjugate addition of arylboronic acids using pyridine-oxazoline **353** as a chiral ligand, giving products **354** with in general good yields and enantioselectivities (Scheme 113). Under these reaction conditions the expected oxidative

Heck reaction was not observed. The model to explain the asymmetric induction is depicted in **TS** in which the aryl group transmetalated *trans* to the *tert*-butyl group of the chiral ligand to avoid steric hindrance.

alt-text: Scheme 113

Scheme 113

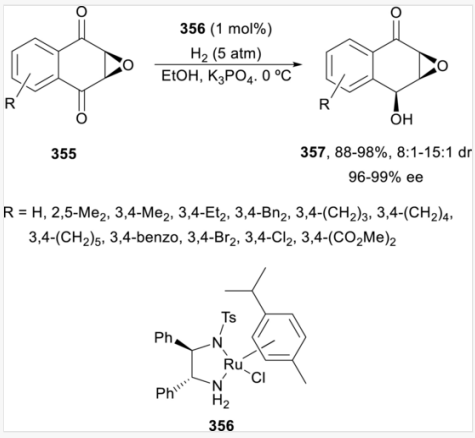


Pd-Catalyzed desymmetrization of norbornenequinones **350** by an enantioselective conjugate addition of arylboronic acids.

Reductive desymmetrization [175] of *cis*-epoxy cyclic ketones **355** has been performed using a combined hydrogenation/transfer hydrogenation process [206]. The resulting *cis*-epoxy naphthoquinols **357** were isolated in very good yields, diastereo- and enantioselectivities (Scheme 114). The Noyori catalyst (*R*,*R*)-TsDPEN-Ru complex **356** was used in ethanol and under H_2 pressure (5 atm) at 0 °C.

alt-text: Scheme 114

Scheme 114

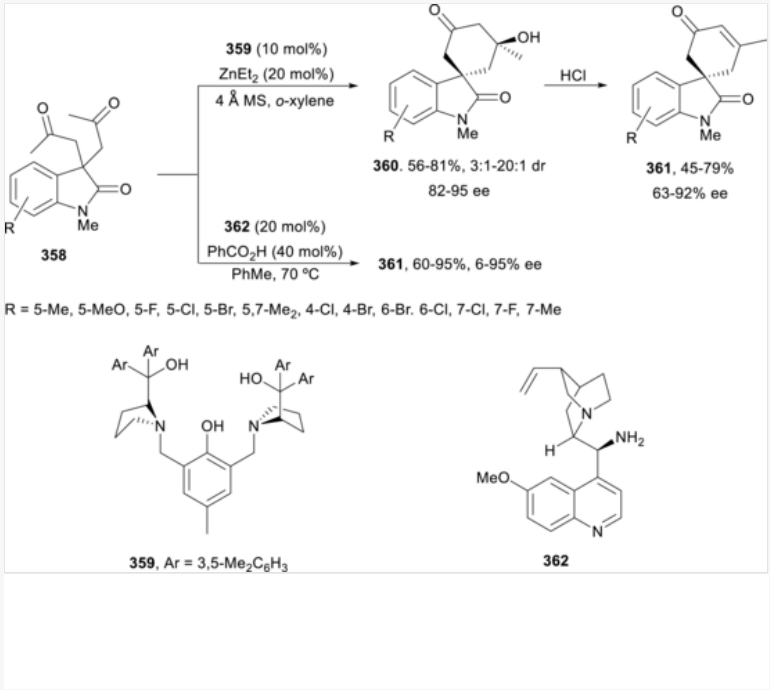


Ru-Catalyzed desymmetrization of *cis*-epoxy diketones **355** by an enantioselective reduction.

Acyclic 1,5-diketones have been desymmetrized by intramolecular aldolizations. List and coworkers [207] described in 2008 the desymmetrization of 4-substituted 2,6-heptanodiones using 9-amino-9-deoxyepiquinine and AcOH as organocatalysts to furnish 5-substituted 3-methyl-2-cyclohexene-1-ones. More recently, Wang and co-workers [208] performed the desymmetrization of oxindole-derived 1,5-diketones **358** by intramolecular aldol reaction catalyzed by a Trost bis-ProPhenol **359** dinuclear zinc complex. The corresponding spiro(cyclohexanone-oxindole) derivatives **360** were obtained in good yields and moderate to good diastereo- and enantioselectivities (Scheme 115). For the preparation of the aldol condensation products **361** aqueous HCl has to be added to the reaction mixture. When this desymmetrization process was carried out with a *Cinchona* alkaloid quinine derived primary amine **362**, instead of the Lewis acid and benzoic acid as co-catalyst, products **361** were directly isolated in high yields and in general excellent enantioselectivities [209].

alt-text: Scheme 115

Scheme 115

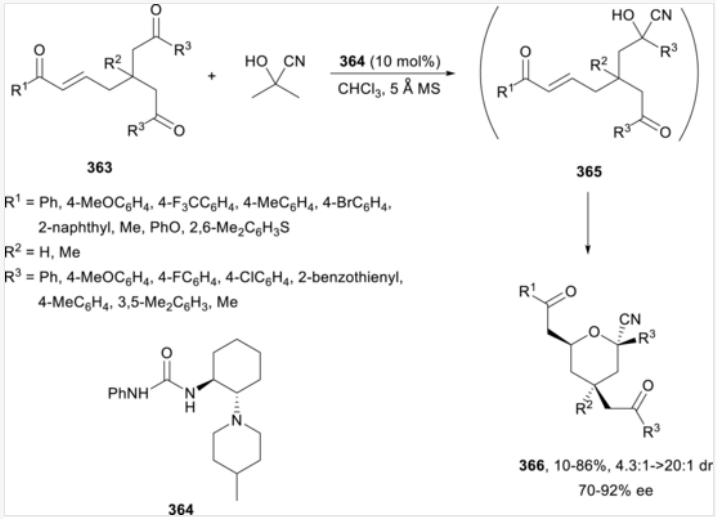


Zn-Catalyzed and organocatalyzed desymmetrization of oxindole-derived 1,5-diketones **358** by an enantioselective intramolecular aldolization.

Cycloetherification of *in situ* generated cyanohydrins has been used by Asano, Matsubara and co-workers [210] for the desymmetrization of 4-substituted 2,6-heptanediones **363**. The reaction of these diketones **363** with acetone cyanohydrin using the urea bifunctional catalyst **364** provide tetrahydropyran derivatives **366** in moderate to good yields and in general good diastereo- and enantioselectivities with up to three stereocenters (Scheme 116). The nucleophilic 1,2-addition step to form cyanohydrins **365** does not determine the observed enantioselectivity, instead the desymmetrization step involves the asymmetric oxy-Michael addition.

alt-text: Scheme 116

Scheme 116



Organocatalyzed desymmetrization of 4-substituted 2,6-heptanediones **363** by an enantioselective cycloetherification of *in situ* generated cyanohydrins.

6 Desymmetrization of dicarboxylic acid derivatives

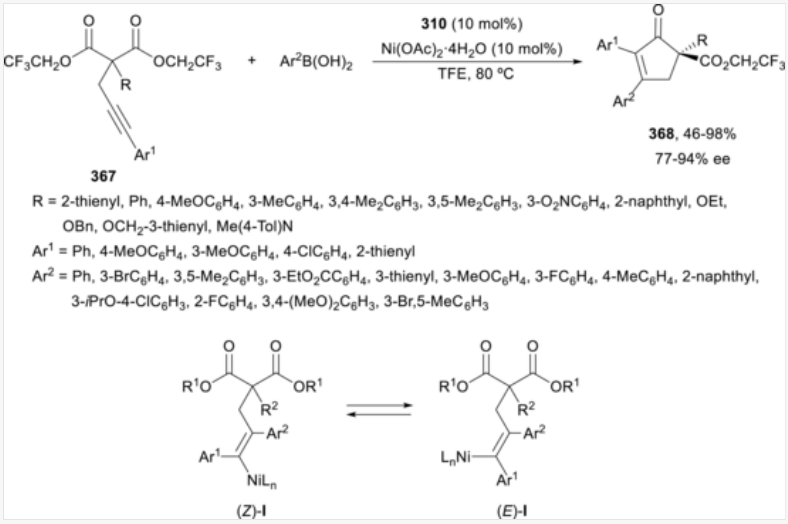
In this section, desymmetrization of diesters by hydrolysis or transesterification, cyclic anhydrides by nucleophilic ring opening, diamides by enzymatic esterification and dinitriles by cyclization reactions will be considered.

6.1 Diesters

2,2-Disubstituted 1,3-diesters or malonates have been submitted to enantioselective hydrolysis catalyzed by enzymes, by chiral phosphoric acid transesterification and by lactamizations [13]. Recent developments involving transition metal catalysis include the asymmetric synthesis of cyclopent-2-enones by Ni-catalyzed desymmetrization of malonate esters bearing an alkynyl moiety at the 2-position **367** by Lam and co-workers [211]. These compounds **367** reacted with arylboronic acids using (*R*)-PhPhos (**310**)/$Ni(OAc)_2$ as catalyst to provide by arylative cyclization cyclopent-2-enones **368** (Scheme 117). The reaction took place by a *syn*-addition of the arylboronic acid to the alkyne giving the (*Z*)-alkenyl species **I**, which by reversible *Z*/*E* isomerization afforded (*E*)-**I**, able to undergo the cyclization.

alt-text: Scheme 117

Scheme 117

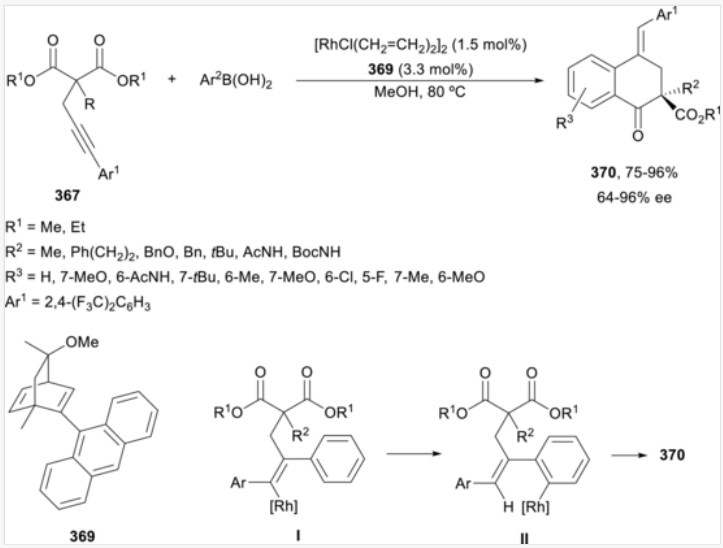


Ni-Catalyzed desymmetrization of 2-alkynylmalonates **367** by an enantioselective arylative cyclization with arylboronic acids.

Alkynyl malonates **367** reacted with arylboronic acids under Rh-catalyzed conditions to yield tetralones **370** by Selmani and Darses [212]. In this case, a chiral diene **369** has been used as ligand for this arylative cyclization (Scheme 118). This cascade reaction took place by regioselective arylrhodium insertion to give intermediate **I** followed by rhodium 1,4-shift affording a new arylrhodium **II** which reacts with one ester group to form the ketone.

alt-text: Scheme 118

Scheme 118

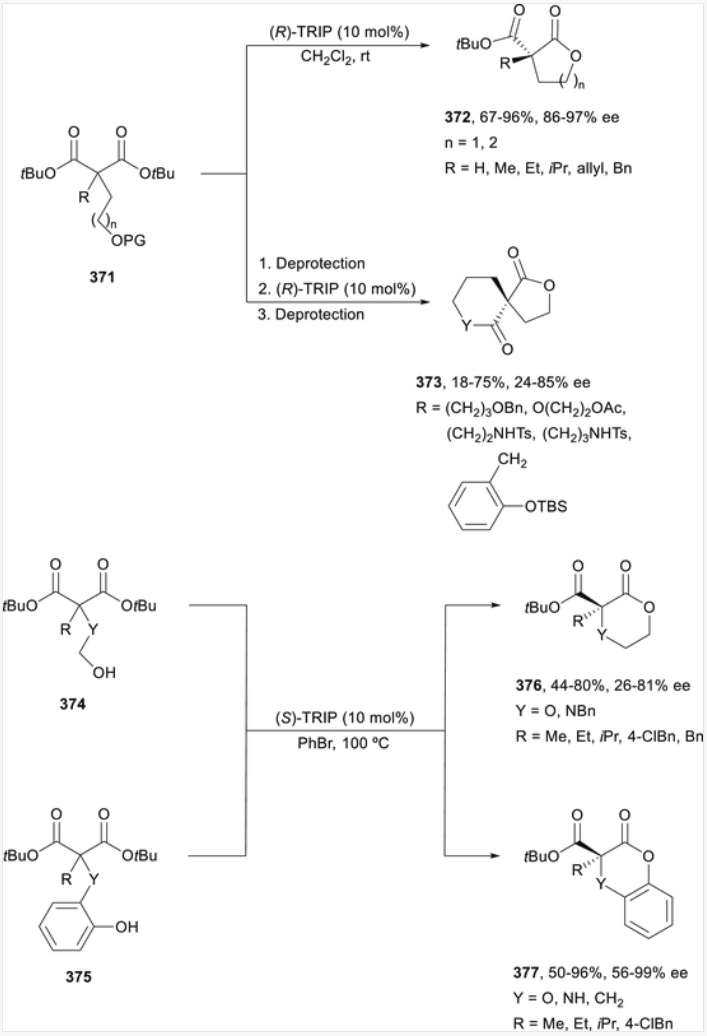


Rh-Catalyzed desymmetrization of 2-alkynylmalonates **367** by an enantioselective arylative cyclization with arylboronic acids.

Petersen and co-workers [213–215] have described chiral phosphoric acid (CPA) catalyzed desymmetrization of malonates **371** bearing a hydroxyethyl moiety at the 2-position. Using (*R*)-TRIP (**200**) as CPA a cyclization took place giving chiral lactones **372** in high yields and enantioselectivities (Scheme 119). When these malonates are bearing an additional functionalized chain a second cyclization took place giving spirocycles **373** [215]. Recently, they applied this strategy to malonates **374** and **375** which afforded dihydrocoumarins and related compounds **376** and **377**, respectively [216].

alt-text: Scheme 119

Scheme 119

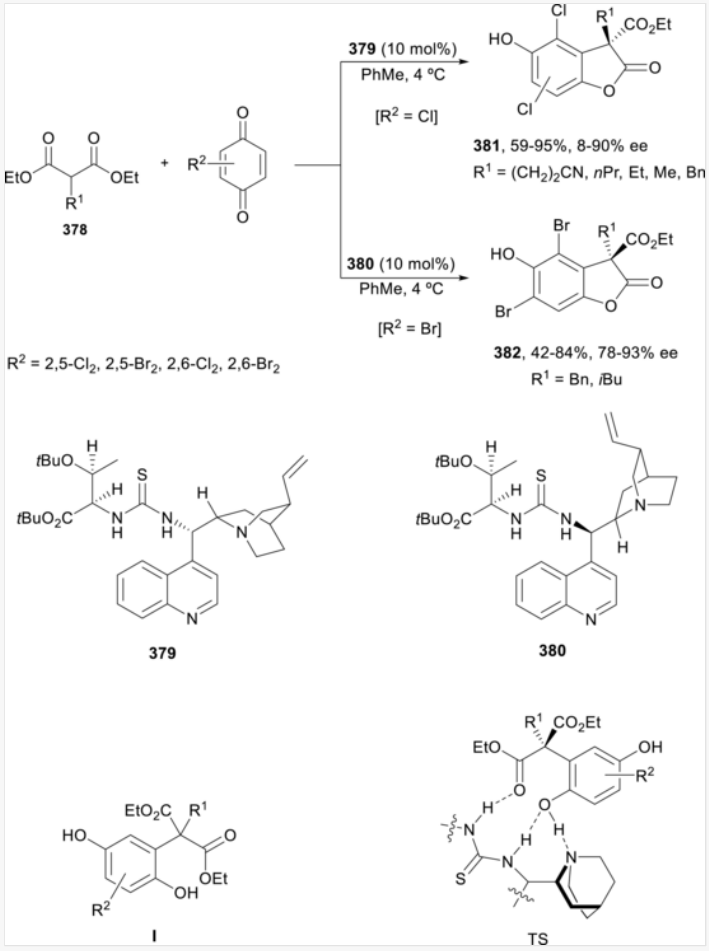


CPA-catalyzed desymmetrization of malonates **371**, **374** and **375** by lactonization.

Another example of desymmetrization of malonates using asymmetric organocatalysis has been reported by Salvio, Bella and co-workers [217]. The addition of 2-substituted diethyl malonates **378** to 1,4-benzoquinones afforded benzofuranones **381** and **382** using thioureas **379** and **380**, respectively (Scheme 120). Yields were considerably increased by portion-wise addition of the quinone. The *Cinchona* derived thioureas **379** and **380** behave as pseudoenantiomers giving products **381** and **382**, respectively. DFT calculations afforded **TS** involving catalyst **379**, in which a double hydrogen bonding interaction between the thiourea and the two oxygen bond atoms of the intermediate **I** occurred.

alt-text: Scheme 120

Scheme 120

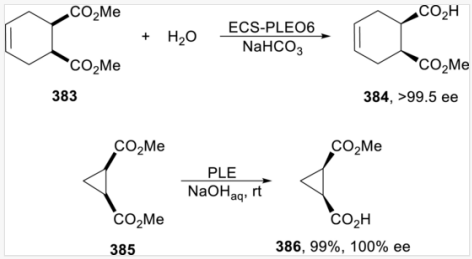


Thiourea-catalyzed desymmetrization of malonates **378** by an enantioselective addition to 1,4-benzoquinones.

Cyclic 1,4-dicarboxylic acid esters have been desymmetrized by fermentative enantioselective saponification with porcine liver esterase (PLE). (1*S*,2*R*)-1-(Methoxycarbonyl)cyclohex-4-ene-2-carboxylic acid (**384**), a pharmaceutical intermediate towards the synthesis of biologically active molecules such as the antibiotic plantecin, anticapsin and (+)-aucantene, has been prepared by desymmetrization of diester **383** by recombinant PLE [218,219]. Due to the poor water solubility of diester **283** Langermann and co-workers [220] found that by dosification of the substrate in a fed-batch manner enzyme ECS-PLEO6 agglomeration was avoided and the complete conversion of *ca*. 75 gL^{-1} of diester was achieved in 3.65 h (Scheme 121). Gaich and co-workers [221] performed the enantioselective synthesis of cyclohepta[*b*]indoles starting from the monoacid **386** as chiral building block. They used the desymmetrization of diester **385** by PLE described previously by Tamm and co-workers [222].

alt-text: Scheme 121

Scheme 121

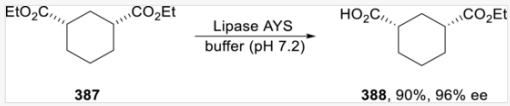


Pig liver esterase-catalyzed desymmetrization of diesters **383** and **385** by an enantioselective hydrolysis.

cis-1,5-Cyclohexanedicarboxylate **387** has been submitted to desymmetrization using lipase AYS Amano in buffer (pH 7.2) to give the monoacid **388** in 90% yield and 96% ee (Scheme 122) [223]. This compound **388** has been used as chiral building block for the synthesis of an azaindolylpyrimidine inhibitor of influenza virus replication.

alt-text: Scheme 122

Scheme 122

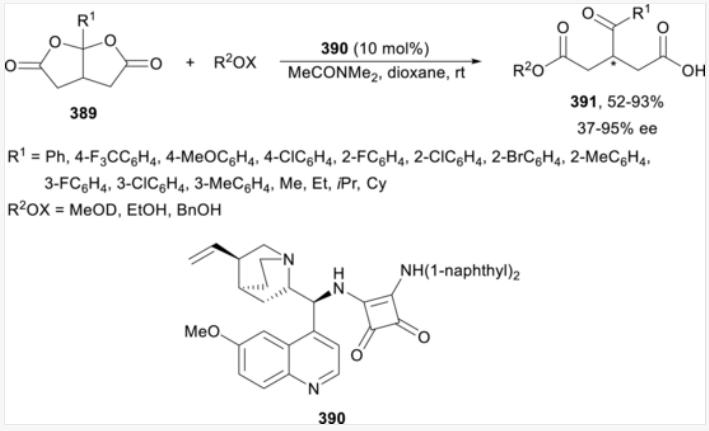


Lipase-catalyzed desymmetrization of 1,5-diester **387** by an enantioselective hydrolysis.

γ,γ-Bislactone-acylals **389**, Fittig's lactones, desymmetrization has been achieved by ring opening with alcohols promoted by *Cinchona* squaramide **390** by Soós and co-workers (Scheme 123) [224]. The resulting glutaric acid derivatives **391** were obtained in general in good yields and enantioselectivities, which are useful chiral building blocks for natural products total synthesis. Hindered alcohols such as isopropanol and *tert*-butanol failed. The absolute configuration of products **391** was not elucidated.

alt-text: Scheme 123

Scheme 123



Organocatalyzed desymmetrization of Fittig's lactones **389** by an enantioselective ring opening with alcohols.

6.2 Anhydrides

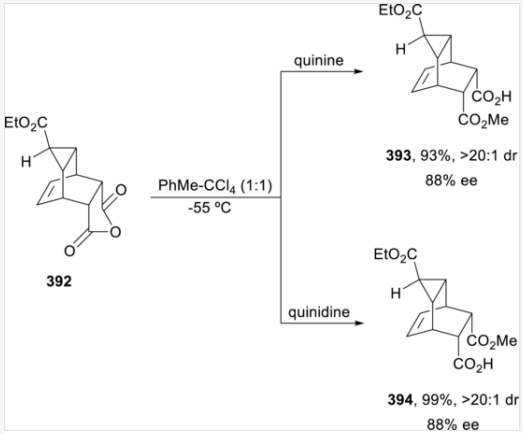
Desymmetrization of *meso*-cyclic anhydrides has been widely studied using nucleophilic ring opening [12,13]. The substrate scope is limited to five or six-membered cyclic systems. Methanolysis of anhydrides using mainly *Cinchona* derived organocatalysts has been extensively applied to the synthesis of pharmaceuticals [12]. The activation of the alcohol by the quinuclidine nitrogen has been proposed.

Recent advances in organocatalyzed desymmetrization by methanolysis of *meso*-anhydride **391** with *Cinchona* alkaloids has been described by Mackay and Johnson [225]. Following the methodology described by Bolm and co-workers [226] they used quinine and quinidine as chiral bases to provide hemieste **393** and **394**, respectively (Scheme 124). The starting anhydride **392** was prepared by Buchner reaction of benzene with ethyl diazoacetate followed by

Diels-Alder reaction with maleic anhydride. Methanolysis of **392** gave products **393** and **394** in very good diastereo- and enantioselectivity working with stoichiometric amounts of bases.

alt-text: Scheme 124

Scheme 124

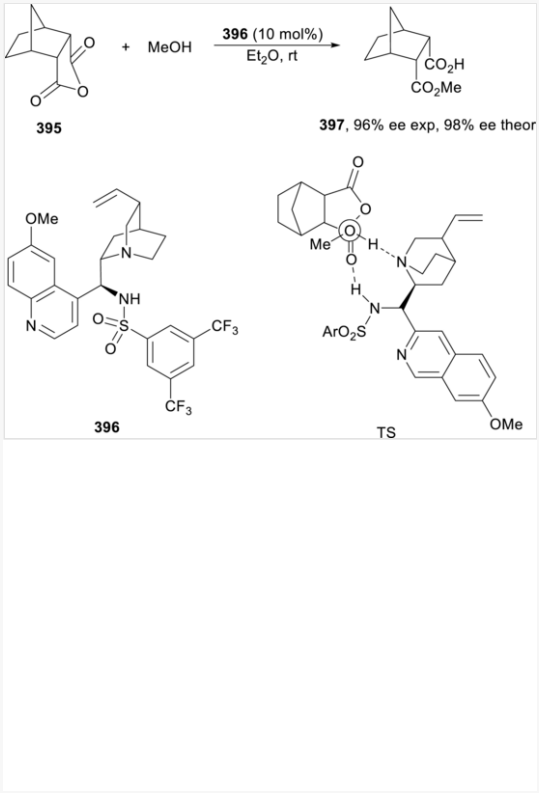


Base-promoted desymmetrization of *meso*-anhydride **392** by an enantioselective methanolysis.

In addition to the native *Cinchona* alkaloids several organocatalysts incorporating thiourea, squaramide or sulfonamide have been employed in desymmetrization of *meso*-anhydrides [12]. The latest reported by Song was very efficient avoiding self-aggregation by hydrogen-bond interactions [227,228]. Recently, a theoretical mechanistic study using quinine sulfonamide organocatalyst **395** for the desymmetrization of *meso*-anhydride **395** to monoester **397** has been carried out by Hofmesiter, Kohen and co-workers (Scheme 125) [229]. They found excellent agreement with the enantioselectivity of this transformation. Theoretical studies about step-wise and concerted pathways concluded that the step-wise one leading to the major enantiomer is more favorable. In the **TS** the quinuclidine nitrogen accepts a hydrogen bond from methanol and the sulfonamide proton stabilized the oxyanionic group by acting as a hydrogen bond donor.

alt-text: Scheme 125

Scheme 125

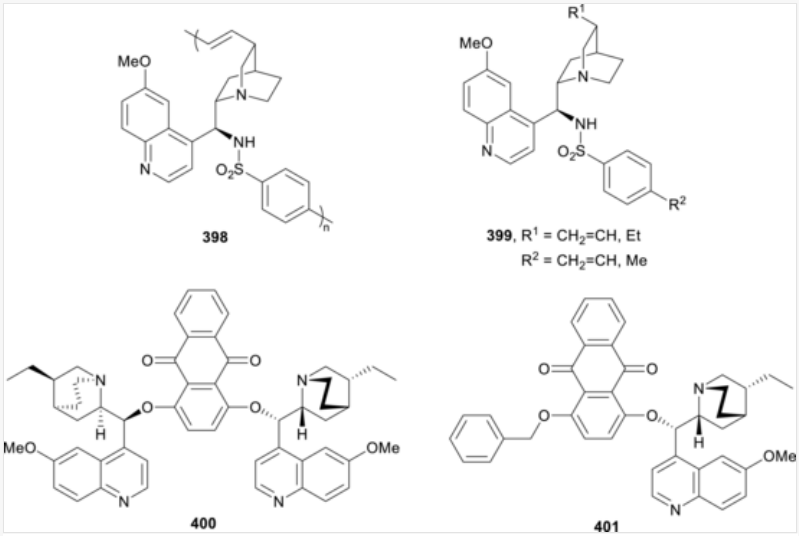


Quinine-sulfonamide-catalyzed desymmetrization of *meso*-anhydride **395** by an enantioselective methanolysis.

This type of *Cinchona* alkaloid sulfonamide has been incorporated into polymers **398** by Mizoroki-Heck polymerization (Fig. 6) [230]. Enantioselective desymmetrization of cyclic anhydrides with **398** by alcoholysis took place in 71–95% ee and the catalyst can be easily separated and reused several times without loss of catalytic activity and enantioselectivity. Rueping and co-workers [231] have prepared microgels with grafted organocatalysts **399** for the alcoholysis of *cis*-tetrahydrophtalic anhydride with ee up to 92% (Fig. 6). This temperature-responsive polymer microgels can be reversibly switched into its soluble or precipitate form and therefore can be easily recovered and reused during at least 10 cycles. D'Anna and co-workers [232] reported the enantioselective alcoholysis of cyclic *meso*-anhydrides using chiral organocatalysts **400** or **401** and ionic liquid gels giving the hemiesters with up to 83% ee.

alt-text: Fig. 6

Fig. 6

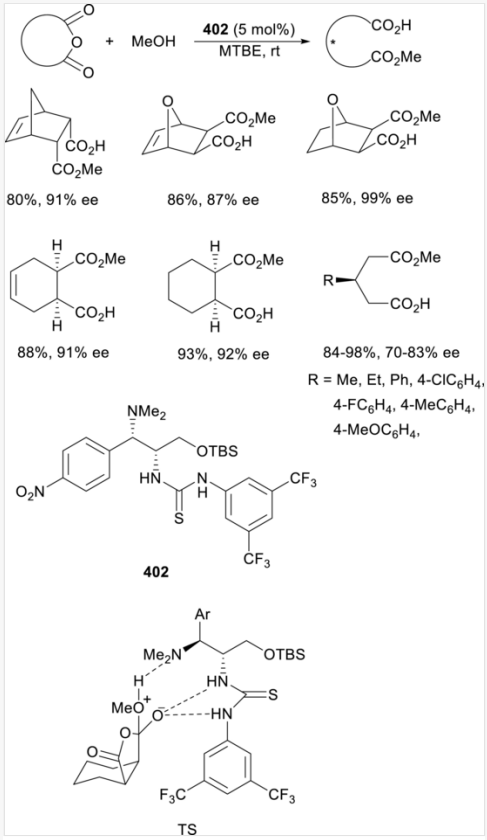


Organocatalysts for anhydrides desymmetrization by enantioselective alcoholysis.

Chloroamphenicol-base-derived-thiourea **402** has been used as chiral organocatalyst for the enantioselective alcoholysis of cyclic *meso*-anhydrides by Chen and co-workers [233]. In Scheme 126 are shown the results for the methanolysis of different anhydrides which gave the corresponding hemiesters in good yields and enantioselectivities (up to 92% ee). In the proposed transition state **TS**, the catalyst forms hydrogen bonding between the tertiary amino group and the protonated ether as well as between the thiourea group and the oxyanion. This method was used for the synthesis of a γ-aminobutyric acid agonist, (*R*)-(−)-baclofen.

alt-text: Scheme 126

Scheme 126

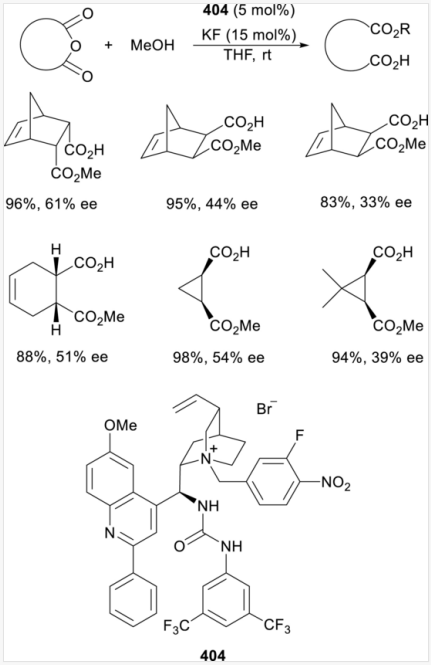


Thiourea-catalyzed desymmetrization of cyclic *meso*-anhydrides by an enantioselective methanolysis.

Enantioselective nucleophilic catalysis by fluoride ions under phase-transfer catalysis has been described by Connon and co-workers [234]. Different cyclic *meso*-anhydrides have been subjected to methanolysis giving the corresponding hemiesters in modest enantiomeric excess (Scheme 127). The quinine-derived ammonium salt **403** and KF in THF at room temperature gave the best results. The mechanistic proposal involves the nucleophilic addition of fluoride to the anhydride to give intermediate **I** followed by ring opening to give intermediate **II** by a cooperation between the hydrogen bond donating urea moiety and the ammonium cation of yhe organocatalyst. Subsequent methanol addition to intermediate **II** provides intermediate **III**, which generates the catalyst and the final hemiester.

alt-text: Scheme 127

Scheme 127

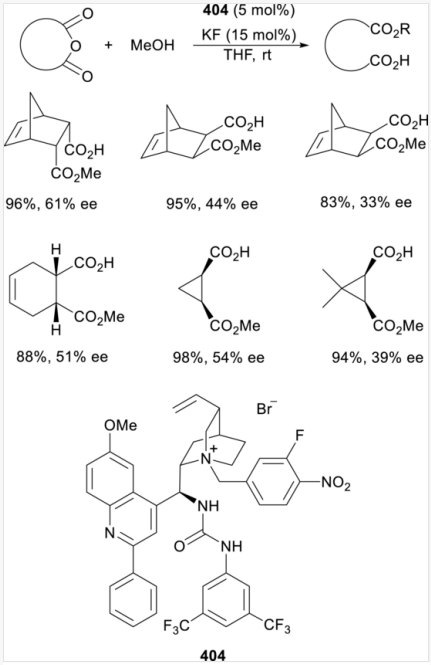


PTC desymmetrization of cyclic *meso*-anhydrides by an enantioselective methanolysis by fluoride ions.

(*R*)-Binaphthyl-based chiral phosphoric acid **404** was used as catalyst for the esterification of cyclic *meso*-anhydrides with benzhydrol or 2,2-diphenylethanol as nucleophiles (Scheme 128) [235]. The resulting hemiesters were obtained in good yields and enantioselectivities working in $CHCl_3$ at room temperature.

alt-text: Scheme 128

Scheme 128



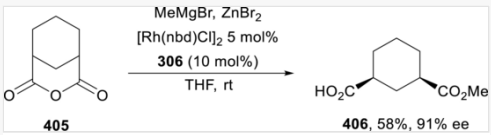
Phosphoric acid-catalyzed desymmetrization of cyclic *meso*-anhydrides by alcoholysis.

The Rh-catalyzed addition of organozinc compounds for desymmetrization of dimethyl glutarate anhydride by Cook and Rovis [236] has been applied as key step in the total synthesis of 6-desmethyl carba-herboxidiene [237]. Enantioselective addition of dimethylzinc to anhydride **405** catalyzed by $[Rh(nbd)Cl]_2$ and (*R*)-*tert*-butylphosphine oxazolidine (**306**) gave the methyl ketone **406** (Scheme 129).

Images are optimised for fast web viewing. Click on the image to view the original version.

alt-text: Scheme 129

Scheme 129



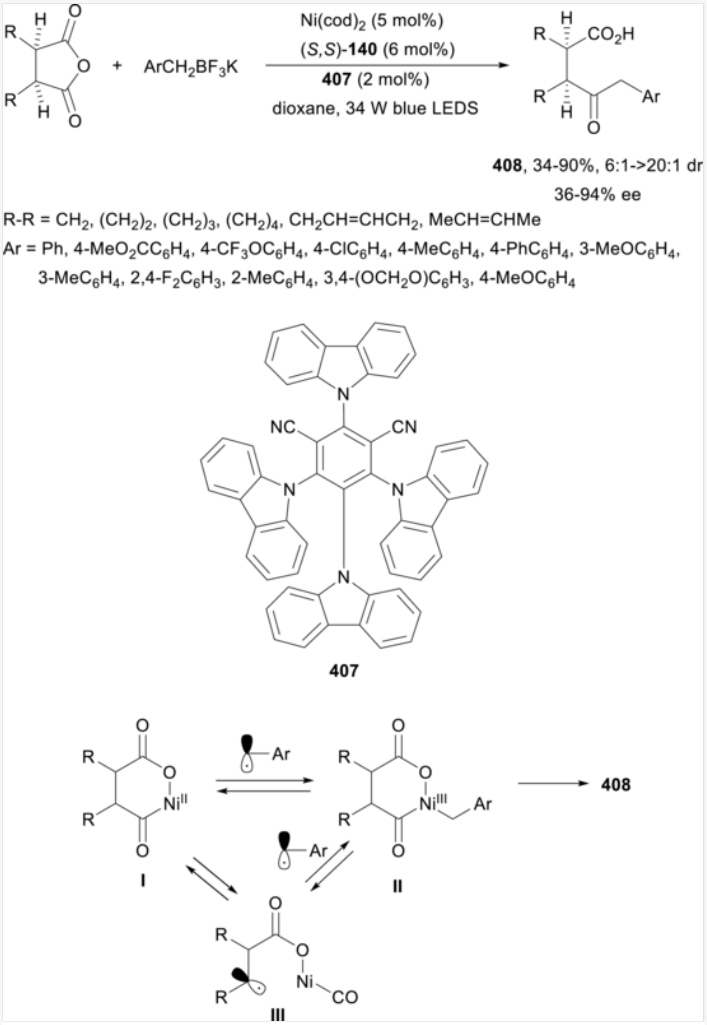
Rh-Catalyzed desymmetrization of *meso*-anhydride by an enantioselective addition of dimethylzinc.

Enantioselective Ni- and photoredox-catalyzed desymmetrization of cyclic *meso*-anhydrides with benzyl trifluoroborates gave mainly the corresponding keto acids **408** (Scheme 130) [238]. (*S,S*)-PhBox (**140**), $Ni(cod)_2$ and

the organophotocatalyst **407** yielded the best results. Instead of the $Ni^{0/I/III}$ mechanism proposed by Molander and Kozlowski [239], Rovis and Doyle have proposed a $Ni^{0/II/III}$ mechanism. The Ni^{II} adduct **I** generates by oxidative addition of Ni^0 to the anhydride followed by interception of the benzylic radical will afford the Ni^{III} intermediate **II**. Subsequent reductive elimination gave the keto acid. The formation of *trans*-products by increasing the Ni loading to 15 mol% has been explained by formation of intermediate **III** by decarbonylation followed by Ni–C bond homolysis.

alt-text: Scheme 130

Scheme 130



Ni and photoredox-catalyzed desymmetrization of cyclic *meso*-anhydrides by an enantioselective cross-coupling with benzyl trifluoroborates.

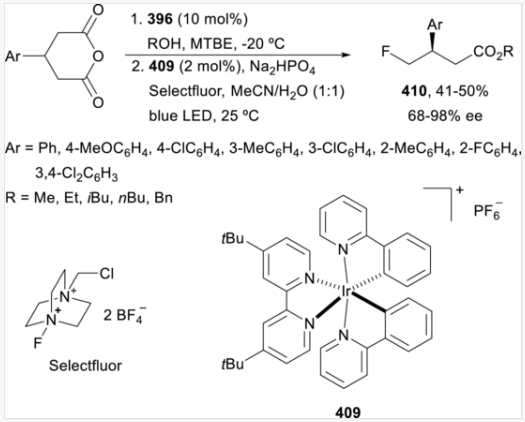
A sequential organocatalyzed desymmetrization by alcoholysis of 3-substituted glutaric anhydrides followed by photoredox-catalyzed decarboxylative fluorination has been reported by Zhao and Yu [240]. Chiral fluorides **410** can

be prepared in moderate yields using *Cinchona* derived sulfonamide **396** as catalyst for the alcoholysis (to give the cooresponding hemiester), the Ir catalyst **409** and Selectfluor for the photoredox fluorination (Scheme 131).

Images are optimised for fast web viewing. Click on the image to view the original version.

alt-text: Scheme 131

Scheme 131



Organocatalyzed desymmetrization/photoredox-catalyzed decarboxylative fluorination of anhydrides.

6.3 Other dicarboxylic acid derivatives

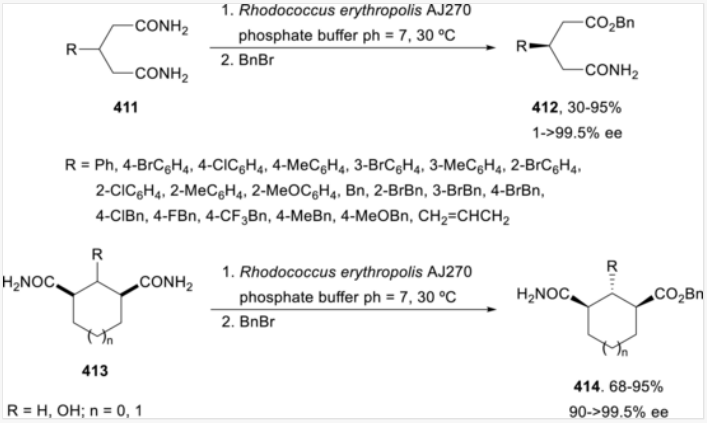
In this section desymmetrization of diamides and dinitriles will be considered. In the case of diamides enzymatic hydrolysis processes are generally used, whereas dinitriles are desymmetrized by metal-catalyzed nucleophilic addition to one of the cyano groups.

Dicarboxamides have been submitted to desymmetrization mainly by enzymatic methods [25]. Lipase-catalyzed hydrolysis in organic solvents has been employed for the desymmetrization of dipyrazolidyl 3-substituted glutarates by Tsai and co-workers [241,242]. Ao and co-workers [243] reported the application of amidasas for general desymmetrization of 3-substituted glutaramides **411**. Biocatalytic hydrolysis with *Rhodococcus erythropolis* AJ270 followed by benzoylation gave 3-substituted glutaric monoester monoamides **412** in up to 95% yield and >99.5 ee (Scheme 132). The same amidase has been used for the desymmetrization of *meso* carboxylic 1,3-dicarboxamides **413** [244] to afford 3-carbamoylcyclic carboxylic acid derivatives **414** in high yields and ee's (Scheme 132). These products **414** have been transformed into chiral bicyclic oxazolidinones.

Images are optimised for fast web viewing. Click on the image to view the original version.

alt-text: Scheme 132

Scheme 132

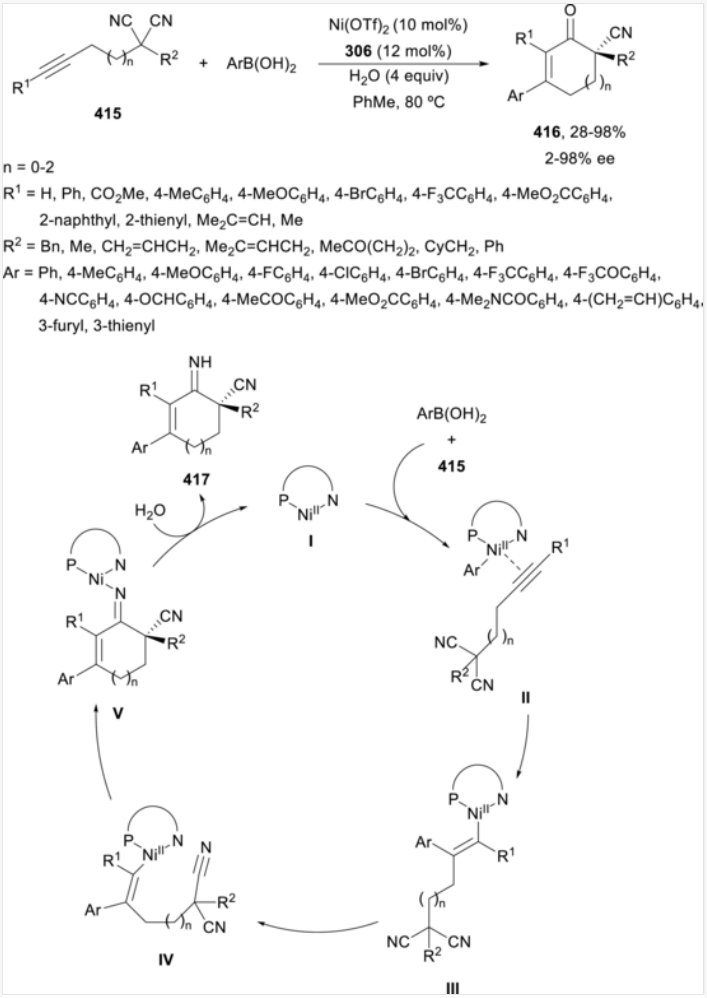


Biocatalytic desymmetrization of 3-substituted glutaramides **411** and 1,3-carboxamides **413** by an enantioselective hydrolysis.

Metal-catalyzed desymmetrization of malononitriles has been recently reported by Liu and co-workers [245]. The Ni-catalyzed addition of arylboronic acids to the alkyne unit of dinitriles **415** followed by nitrile insertion gave 5–7 membered cyclohexenones **416** using tBuPhox (**306**) as a chiral ligand in moderate to good enantioselectivities (Scheme 133). Mechanistic experiments support the catalytic cycle in which the catalyst **I** underwent transmetalation with the arylboronic acid to generate the alkylnickel species **II**. Insertion of the alkyne in the Ni–C bond formed the *cis*-alkenynickel **III**, which after *cis/trans* isomerization provided the *trans*-species **IV**. Addition to one of the cyano groups delivered the iminylnickel **V**, which underwent protonation to furnish the imine **417**, precursor of the cycloalkenones **416**, and the catalyst.

alt-text: Scheme 133

Scheme 133

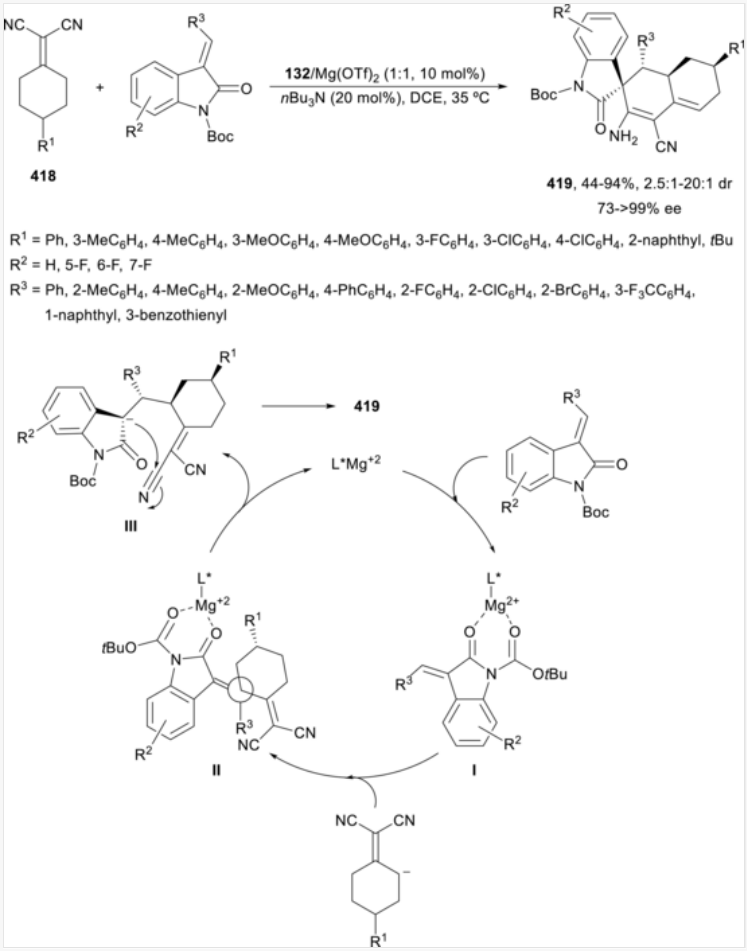


Ni-Catalyzed desymmetrization of alkynylmalononitriles **415** by an enantioselective addition of arylboronic acids and cyclization.

Cyclic α,α-dicyanoalkenes **418** have been submitted to desymmetrization by vinylogous Michael addition to *N*-Boc-protected alkylideneindolinones followed by cyclization to yield spiroindolinones **419** with excellent diastereo- and enantioselectivities (Scheme 134). Feng and co-workers [246] used the *N*,*N*′-dioxide **132**/$Mg(OTf)_2$ complex as chiral catalyst able to coordinate the two carbonyl groups of the alkylideneindolinone. In the proposed catalytic cycle conjugate addition of deprotonated α,α-dicyanoalkene to intermediate **I** gave **II**, which evolved to the Michael adduct **III**. Intramolecular addition to one of the cyano groups afforded spiroindolinone **419**.

alt-text: Scheme 134

Scheme 134



N,N′-Dioxide **132**/Mg(OTf)$_2$-catalyzed desymmetrization of α,α-dicyanoalkenes **418** by enantioselective vinilogous Michael addition to alkylideneindolinones and cyclization.

7 Desymmetrization of carbocyclic compounds

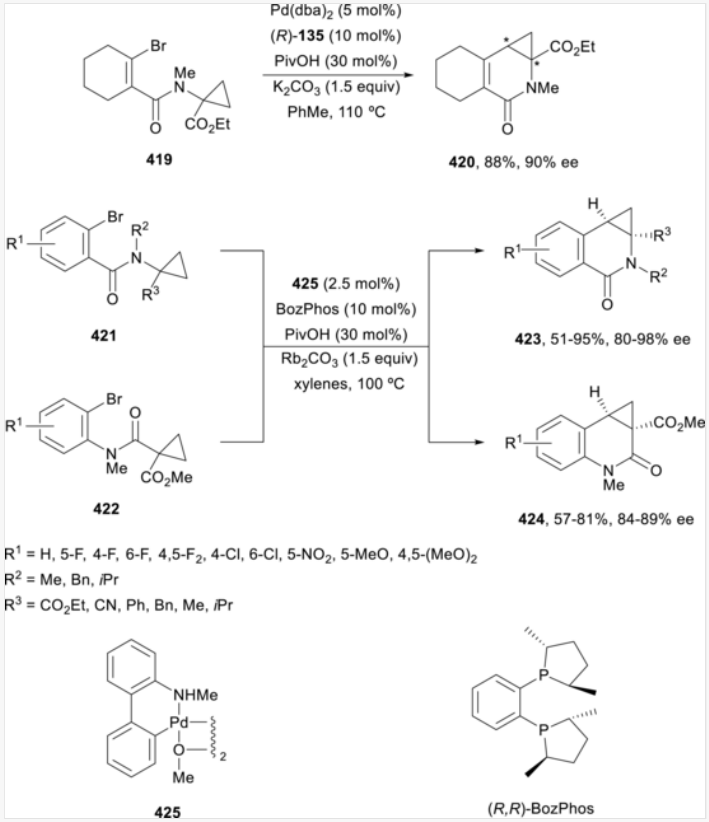
In this section, enantioselective desymmetrization of small-ring systems such as cyclopropanes and cyclopropenes, cyclobutanes and cyclobutenes as well as five and six-membered cyclic compounds will be considered.

7.1 Cyclopropanes

Metal-catalyzed C–H functionalization of cyclopropanes has been carried out mainly by Pd-catalysis allowing desymmetrization of 1,1-disubstituted cyclopropanes. Ladd and Charette [247] described an intramolecular sp^3 functionalization of cyclopropyl α-amino acid derived benzamides **419** under Pd catalysis using Feringa's phosphoramidite **135** as a chiral ligand to provide **420** in 88% yield and 90% ee (Scheme 135). After these preliminary results the same group [248] employed (*R,R*)-BozPhos as an effective chiral ligand for the enantioselective cyclization of benzamides **421** and acylated anilines **422** to a broad spectrum of dihydroisoquinolines **423** and dihydroquinolines **424**, respectively, in good yields and enantioselectivities (Scheme 135). In this case Buchwald's fourth generation dimer **425** [249] gave the best results.

alt-text: Scheme 135

Scheme 135



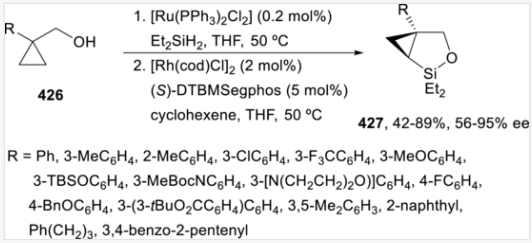
Pd-Catalyzed desymmetrization of 1,1-disubstituted cyclopropanes by an enantioselective intramolecular C–H functionalization.

Intramolecular Rh-catalyzed enantioselective silylation of 1-substituted cyclopropylmethanols **426** has been described by Lee and Hartwig [250]. Silylation of cyclopropyl C–H bonds took place by *in situ* formation of hydrosilyl ethers by Ru-catalyzed reaction with diethylsilane followed asymmetric Rh-catalyzed silylation using (*S*)-DTBM-Segphos as bidentate chiral ligand to afford oxasilolanes **427** (Scheme 136). According to kinetic isotope effect experiments the C–H cleavage may be the turnover-limiting step. These products were obtained in good yields and ee's, which are suitable substrates for the Tamao-Fleming oxidation to form cyclopropanols.

Images are optimised for fast web viewing. Click on the image to view the original version.

alt-text: Scheme 136

Scheme 136



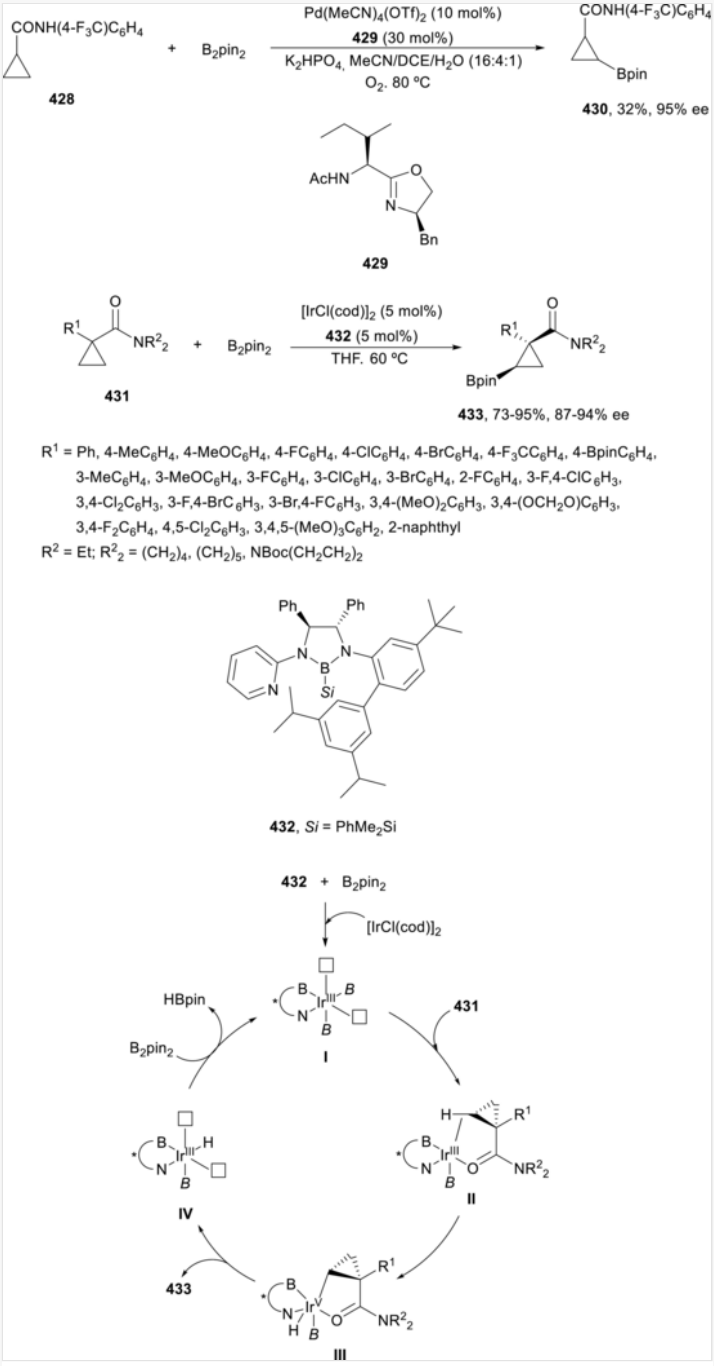
Rh-Catalyzed desymmetrization of 1-substituted cyclopropylmethanols **426** by an enantioselective intramolecular silylation.

Yu and co-workers [251] reported the enantioselective intermolecular borylation of different carbocyclic amides under Pd-catalysis. Using aminomethyl oxazoline ligand **429**, cyclopropanecarboxylic amide **428** was borylated to give **430** (absolute configuration not determined) in 32% yield and 95% ee (Scheme 137). Further studies by Xu and co-workers [252] on borylation reactions established that 1-substituted cyclopropanecarboxamides **431** can be transformed diastereoselectively into *cis*-borylated products **433** under Ir-catalysis using a chiral bidentate ligand **432** in very good yields and enantioselectivities (Scheme 137). In the proposed mechanism, intermediate **I** with two available vacant coordination sites reacted with the substrate **431** to give intermediate **II** in which one of the β-C–H bonds of the

cyclopropane unit is preactivated by an agostic interaction with the Ir(III) center. Oxidative addition of this C–H bond afforded intermediate **III**, which by reductive elimination resulted product **433** and an Ir(III) hydrido boryl complex **IV**. Final reaction of **IV** with B_2pin_2 regenerated intermediate **I**.

alt-text: Scheme 137

Scheme 137

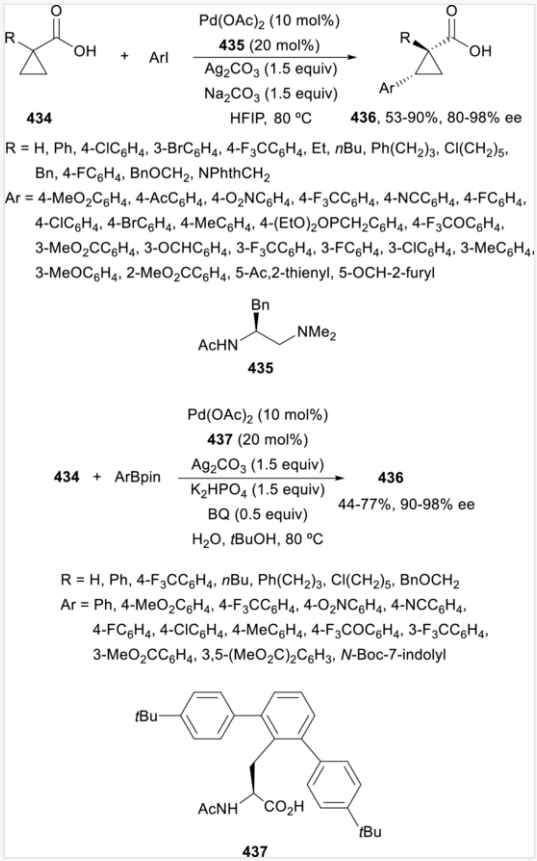


Pd and Ir-Catalyzed desymmetrization of cyclopropanecarboxamides **428** and **431** by an enantioselective borylation.

Intermolecular C–H arylation of unsubstituted and 1-substituted cyclopropanecarboxylic acids **434** has been performed under Pd-catalysis by Yu and co-workers [253]. The enantioselective arylation took place with aryl iodides and diamine **435** as a chiral ligand in hexafluoroisopropanol (HFIP) to provide *cis*-β-arylated cyclopropanecarboxylic acids **436** in good yields and enantioselectivities (Scheme 138). The same group reported the arylation of these substrates **434** with arylboronates ArBpin under Pd-catalysis using 2,6-disubstituted phenylalanine derived ligand **437** in the presence of benzoquinone (BQ) [254]. This process was also performed with vinyl boronates to give the corresponding 2-alkenyl cyclopropanecarboxylic acids.

alt-text: Scheme 138

Scheme 138

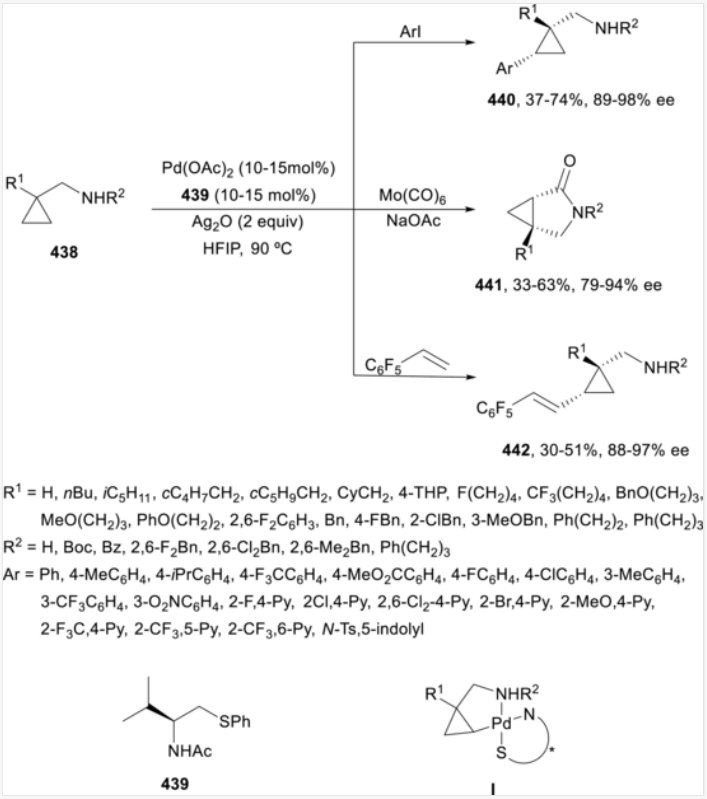


Pd-Catalyzed desymmetrization of cyclopropanecarboxylic acids **434** by an enantioselective arylation with aryl iodides and with arylboronates.

A recent example on desymmetrization by Pd-catalyzed enantioselective C–H functionalization of cyclopropylmethylamines **438** has been reported by Zhang and Yu [255]. Arylation with aryl and heteroaryl iodides, carbonylation and olefination reactions were performed using a chiral bidentate thioether ligand **439** to afford products **440–442** in moderate yields and high ee's (Scheme 139). Both Pd(II)/Pd(IV) and Pd(II)/Pd(0) catalytic cycles can operate in these transformations by participation of palladacycle **I**.

alt-text: Scheme 139

Scheme 139

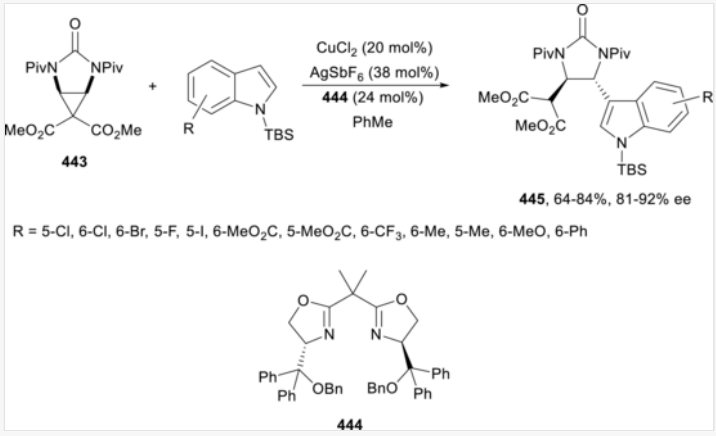


Pd-Catalyzed desymmetrization of cyclopropylmethylamines **438** by an enantioselective C–H activation, carbonylation and alkenylation reactions.

Waser and co-workers [256] have performed the enantioselective desymmetrization of *meso*-diaminocyclopropanes **443** by copper(II)-catalyzed Friedel-Crafts alkylation of indoles using a chiral Box ligand **444**. The corresponding urea products **445** are structurally related to natural and synthetic bioactive compounds and were obtained in high diastereo and enantioselectivities with *trans*-configuration according to a S_N2-like mechanism for the ring opening of the cyclopropane (Scheme 140).

alt-text: Scheme 140

Scheme 140



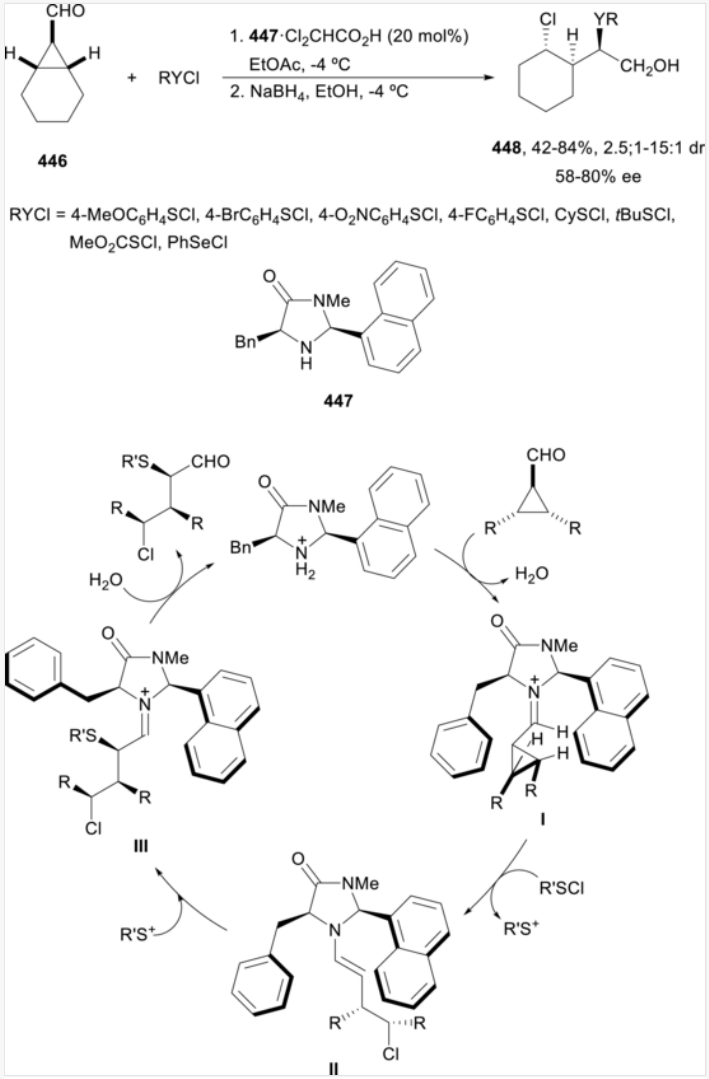
Cu-Catalyzed desymmetrization of *meso*-diaminocyclopropanes **443** by an enantioselective Friedel-Crafts alkylation of indoles.

Iminium-enamine activation has been used for the desymmetrization of cyclopropylcarbaldehydes **446** by Werz and co-workers [257]. Based on previous work of Sparr and Gilmour [258] on asymmetric 1,3-dichlorination, they employed sulfenyl and selenyl chorides. In the case of cyclopropylcarbaldehyde, products of type **448** were obtained using a second generation of MacMillan organocatalyst **447** following by reduction of the aldehyde with $NaBH_4$ (Scheme 141

). In the proposed mechanism the initial step is the formation of the iminium ion **I**, which is attacked by the chloride from the sulfenyl chloride to form the enamine **II** and the sulfenylium ion. In **II** the benzyl group shielded the top face giving by attack of the sulfenium ion the iminium complex **III**.

alt-text: Scheme 141

Scheme 141



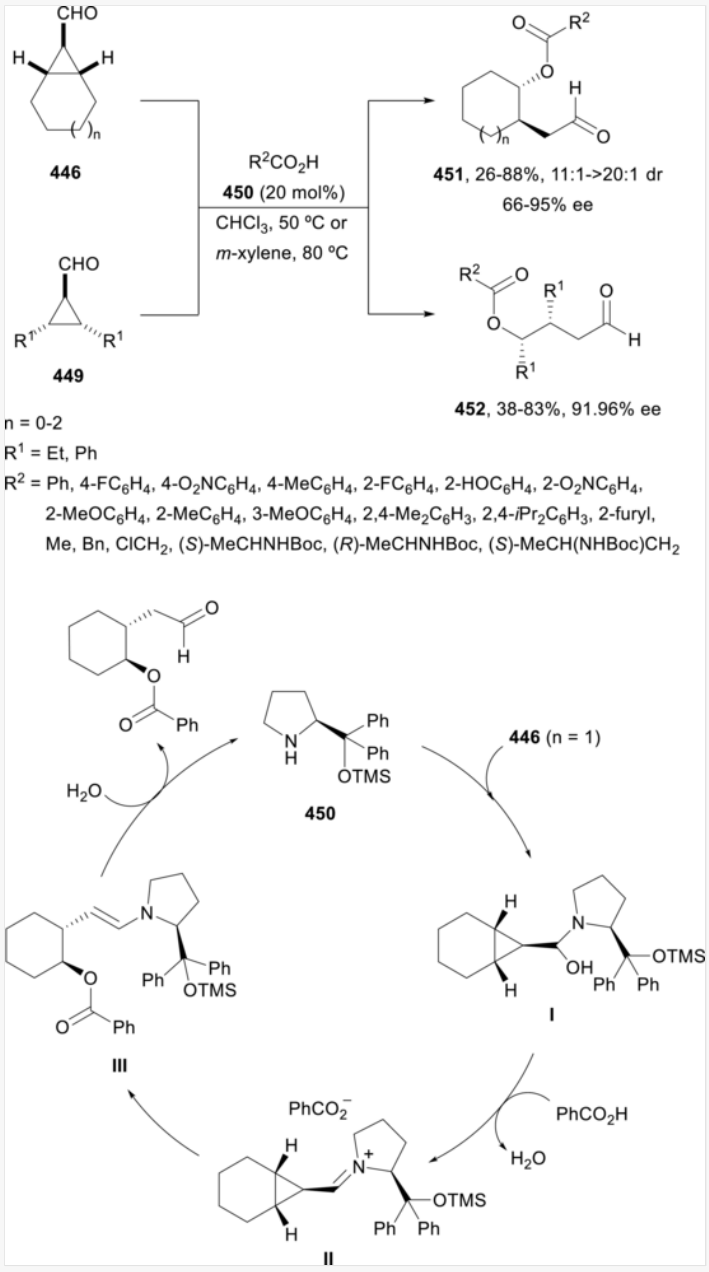
Organocatalyzed desymmetrization of cyclopropylcarbaldehydes **446** by an enantioselective 1,3-chlorochalcogenation.

Merino, Vicario and co-workers [259] used carboxylates as nucleophiles for the ring opening of *meso*-cyclopropanecarbaldehydes **446** and **449** using diarylprolinol derivative **450** as organocatalyst (Scheme 142). The

resulting products **451** and **452** were isolated in good yields, diastereo- and enantioselectivities. According to DFT calculations a catalytic cycle involving the formation of hemiaminal **I** and the iminium ion **II** promoted by participation of benzoic acid. Final attack of benzoate gave intermediate **III** by a S_N2-type reaction affording the catalyst and **451**. This process has been applied to the synthesis of speciosin H, a metabolite isolable from the basidiomycete fungus *Hexagonia speciosa*.

alt-text: Scheme 142

Scheme 142



Organocatalyzed desymmetrization of cyclopropanecaraldehydes **446** and **449** by an enantioselective ring opening with carboxylates.

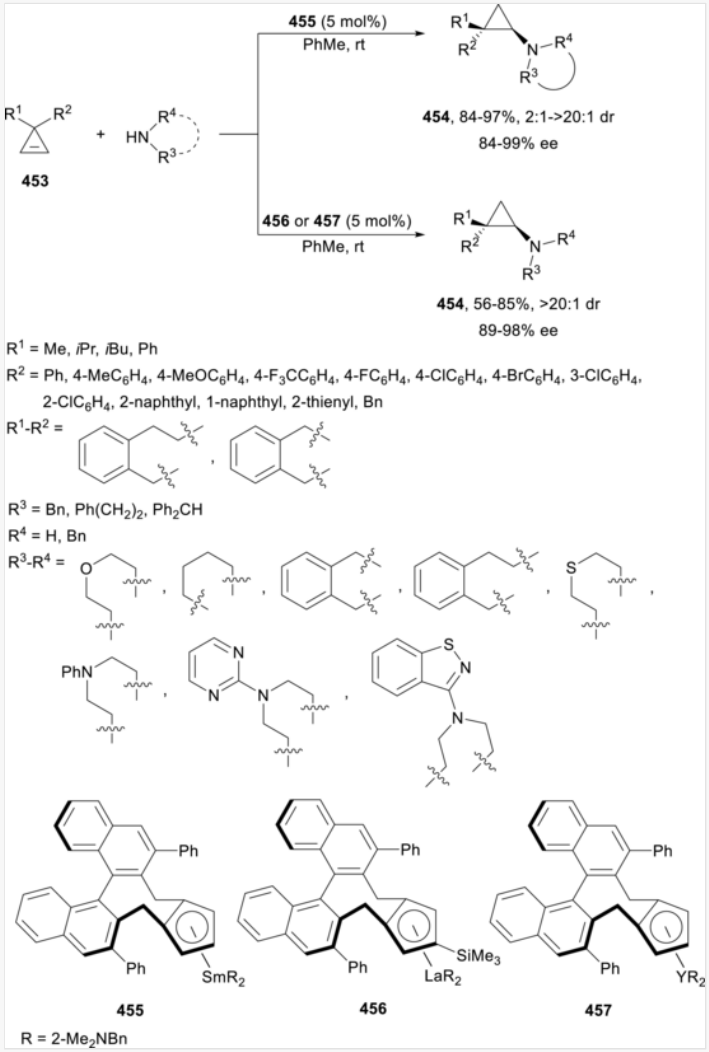
7.2 Cyclopropenes

Two basic methods have been developed for desymmetrization of cyclopropenes, the enantioselective addition to the C=C and ring opening/cross metathesis under transition-metal catalysis [13]. Recent desymmetrization methods are based mainly in enantioselective additions. Hydroamination of substituted cyclopropenes **453** with secondary aliphatic amines catalyzed by chiral half-sandwich rare-earth metal complexes gave the corresponding aminocyclopropenes **454** in high yields, diastereo- and enantioselectivities (Scheme 143) [260]. In the case of cyclic amines the Sm complex **455**

gave the best results, whereas for acyclic amines La and Y complexes **456** and **457** afforded products **454**, respectively, with higher enantioselectivities. In the case of catalyst **455** a favored **TS** has been proposed for the enantioselective hydroamination.

alt-text: Scheme 143

Scheme 143



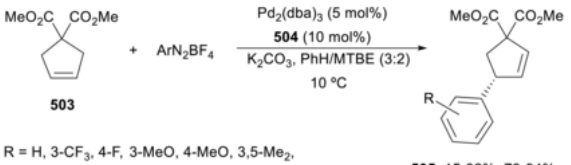
Rare-earth-metal-catalyzed desymmetrization of cyclopropenes **453** by an enantioselective hydroamination.

Copper-catalyzed Cope-type hydroamination of cyclopropenes **453** has been performed by Zhang and co-workers [261] using oximes as nucleophiles, so nitrones **458** were obtained (Scheme 144). This enantioselective desymmetrization was carried out with (*R*)-DTBM-Segphos as a chiral ligand giving products **458** and **459** in high yields, diastereo- and enantioselectivities with different benzophenone oximes as well as aldoximes. From experimental mechanistic studies it was proposed a plausible catalytic cycle in which the oxime ligated Cu(I) species **I** coordinates cyclopropene **453** (R^1 = Ph; R^2 = Me) to form complex **II**. This complex undergoes migratory insertion to give cyclopropyl copper **III** after a five-membered metala-retro-Cope transition state **TS**. Protonation of **III** with the oxime (path a) or with *t*BuOH (path b) releases the nitrones.

alt-text: Scheme 144

Scheme 144

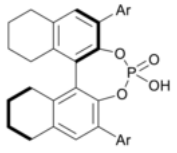
Scheme 144



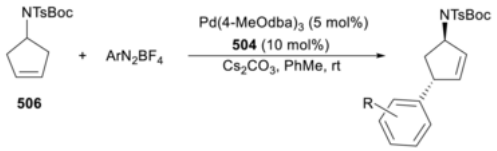
503

R = H, 3-CF_3, 4-F, 3-MeO, 4-MeO, 3,5-Me_2, 4-*t*Bu, 4-Ph, 3-Cl, 2-F

505, 15-82%. 79-94% ee



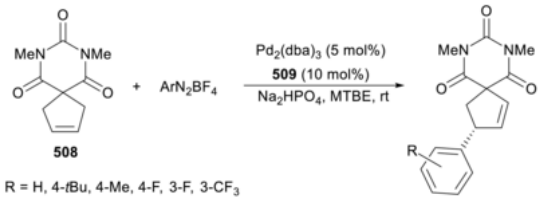
504, Ar = 2,4,6-$Cy_3C_6H_2$



506

R = 4-F, 3,5-Me_2, 4-Ph, 3-MeO

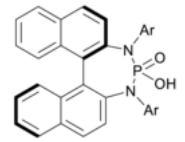
507, 53-86%, 83-90% ee



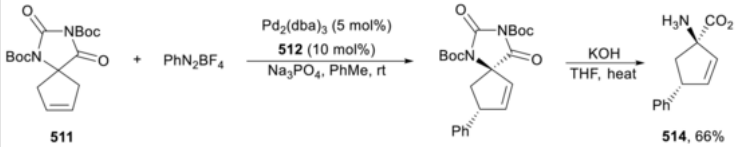
508

R = H, 4-*t*Bu, 4-Me, 4-F, 3-F, 3-CF_3

510, 67-94%, 84-92% ee



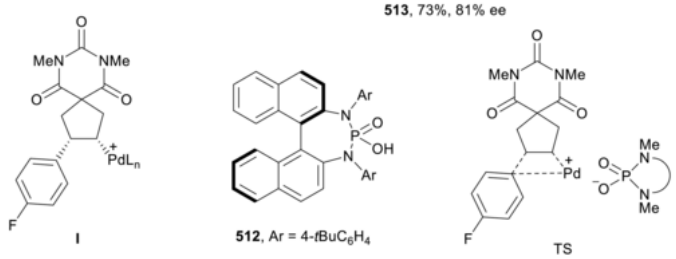
509, Ar = 4-adamantylC_6H_4



511

513, 73%, 81% ee

514, 66%



I

512, Ar = 4-*t*BuC_6H_4

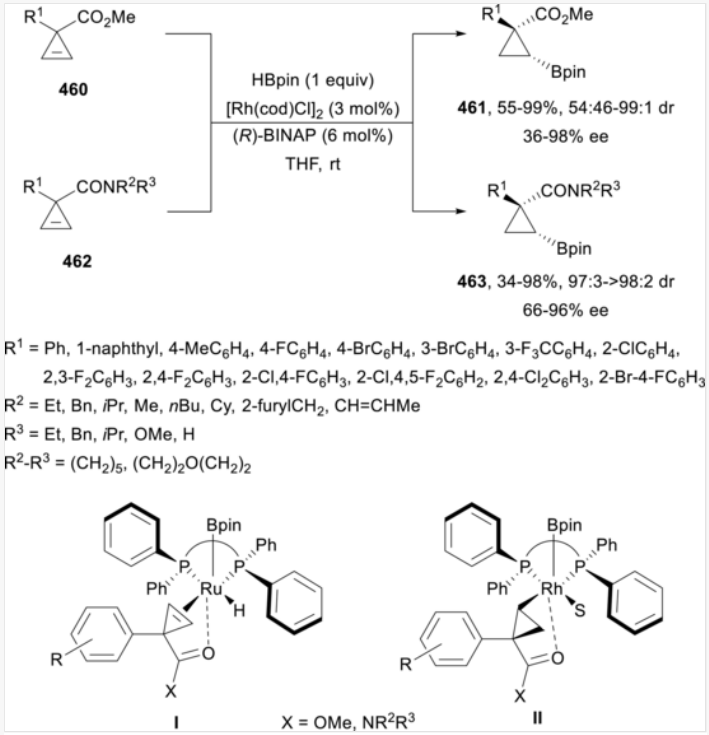
TS

Cu-Catalyzed desymmetrization of cyclopropenes **453** by an enantioselective hydronitroylation with oximes.

Hydroboration of cyclopropenes provided cyclopropylboronates under Rh [262] catalysis directed by a carboxylate group. Recently the same group described that a carboxamide functionality is an alternative superior directing group [263]. In the case of methyl 1-arylcyclopropane carboxylates **460** with *ortho*-halogen substituted aryl groups, the hydroboration to products **461** took place in lower yields and poor diastereo- and enantioselectivities because of additional coordination with Ru. In contrast, amide directing groups in compounds **462** allowed stronger chelation to Rh giving products **463** with higher stereoselectivities (Scheme 145). The observed enantioselectivity can be attributed to the predominant formation of the octahedral Ru(III)-complex **I** with minimal steric interactions between the phenyl rings of the BINAP ligand and the substrate giving cyclopropylrhodium complex **II**.

alt-text: Scheme 145

Scheme 145

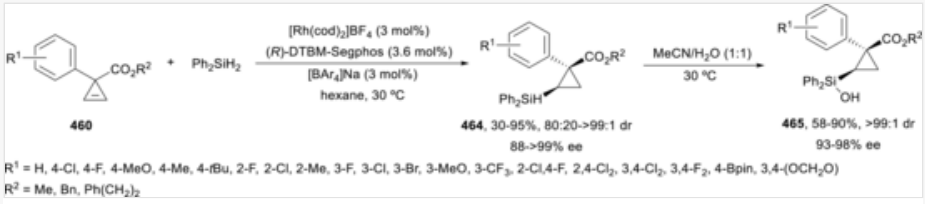


Rh-Catalyzed desymmetrization of cyclopropene carboxylates **460** and carboxamides **462** by an enantioselective hydroboration.

Rh-Catalyzed desymmetrization by hydrostannation of cyclopropenes was initially described by Gevorgyan and co-workers [264] using Trost ligand. Recently, Xu and co-workers [265] reported the Rh-catalyzed hydrosilylation of cyclopropenecarboxylates **460** using chiral (*R*)-DTBM-Segphos as ligand. When the reaction was carried out with diphenylsilane, products **464** were obtained in high yield, diastereo- and enantioselectivities (Scheme 146). Using other silanes $R^1R^2SiH_2$ a new silicon stereogenic center can be generated with poor diastereoselectivity. Tandem hydrosilylation/oxidation gave cyclopropylsilanols **465** in high yields, diastereo- and enantioselectivities.

alt-text: Scheme 146

Scheme 146

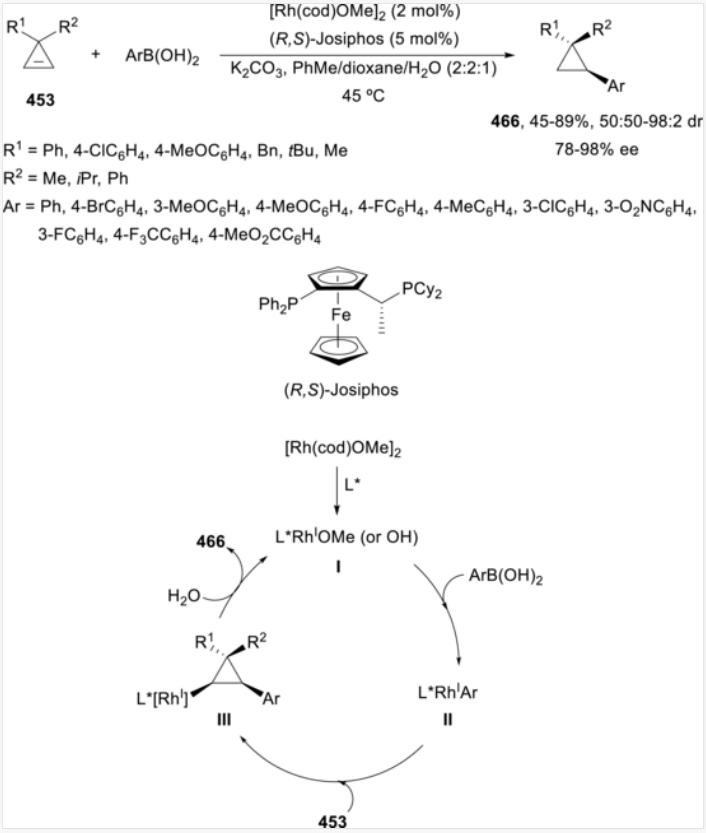


Rh-Catalyzed desymmetrization of cyclopropenecarboxylates **460** by an enantioselective hydrosilylation.

Dian and Marek [266] reported the Rh-catalyzed enantioselective arylation for desymmetrization of non-functionalyzed cyclopropenes **453**. Arylboronic acids in the presence of (*R,S*)-Josiphos as a chiral ligand gave products **466** in good yields and high diastereo- and enantioselectivities (Scheme 147). In the proposed reaction mechanism the organorhodium species **II** can be formed by transmetalation between the alkylboronic acid and the Rh complex **I**. This intermediate **II** stereoselectively adds to the cyclopropene to provide the species **III**, which is hydrolyzed *in situ* to form the final product and regenerates **I**.

alt-text: Scheme 147

Scheme 147

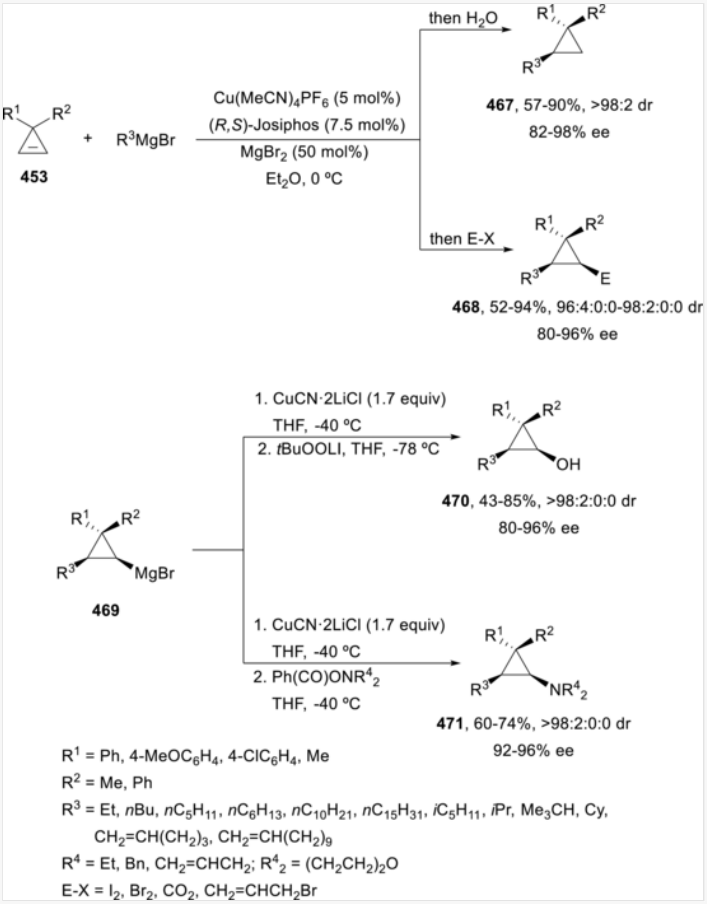


Rh-Catalyzed desymmetrization of non-functionalized cyclopropenes **453** by an enantioselective hydroarylation with arylboronic acids.

Müller and Marek [267] have described the copper-catalyzed carbozincation of cyclopropenes **453** using (*R*)-DTBM-Segphos as a chiral ligand. This carbometalation process [268] can be also performed for the enantioselective desymmetrization of cyclopropenes **453** using the most easily accessible alkyl Grignard reagents and (*R,S*)-Josiphos as a chiral ligand [269] (Scheme 148). The corresponding cyclopropenes **467** were obtained with excellent stereoselectivities. Intermediate cyclopropylmetal species are configurationally stable and the C–Mg bond reacts with different electrophiles to provide polysubstituted cyclopropanes **468**. When intermediate cyclopropylmagnesium compounds **469** were allowed to react with CuCN·2LiCl resulted, by oxidation with *t*BuOOLi or by amination with *O*-benzoyl hydroxylamines, the corresponding cyclopropanols **470** or cyclopropylamines **471**, respectively (Scheme 148) [270].

alt-text: Scheme 148

Scheme 148



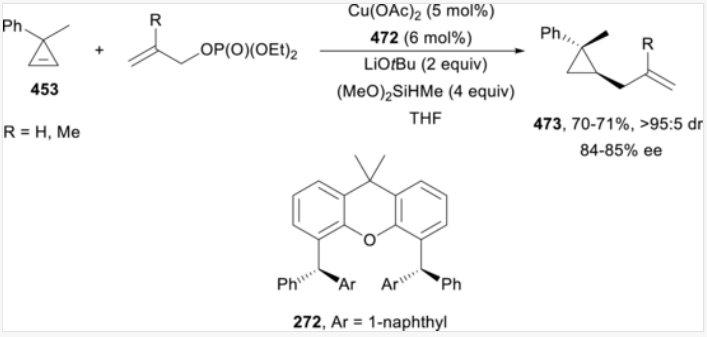
Cu-Catalyzed desymmetrization of cyclopropenes **453** by an enantioselective carbomagnesiation.

The same group described the copper-catalyzed hydroallylation of cyclopropene **453** with allyl phosphates [271]. An enantioselective hydroallylation was possible using a chiral Xantphos derivative **472** as ligand (Scheme 149). Products **473** were obtained with good yields and stereoselectivities. The carbometalation of cyclopropane **453** took place by formation of a cyclopropylcopper intermediate **I** that would be trapped by the allylic electrophile with retention of the configuration.

Images are optimised for fast web viewing. Click on the image to view the original version.

alt-text: Scheme 149

Scheme 149

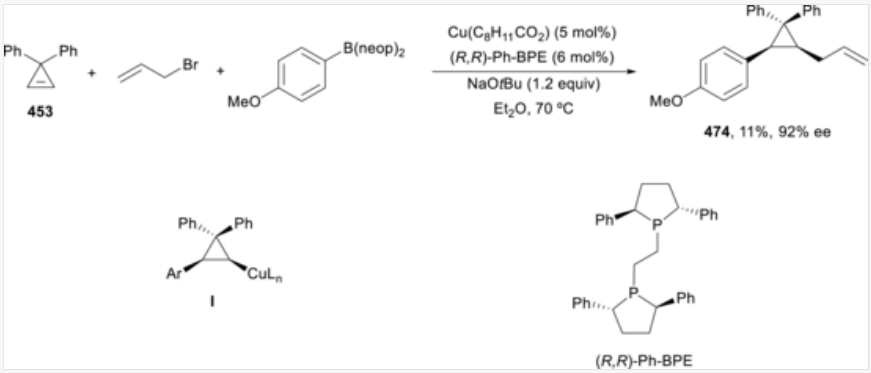


Cu-Catalyzed desymmetrization of cyclopropene **453** by an enantioselective hydroallylation with allyl phosphates.

Zhang and co-workers reported a three-component cyclopropene carboallylation [272]. Organoboron cyclopropenes **453** and allyl bromide reacted under Cu-catalysis to give stereoselectively difunctionalized cyclopropanes. Preliminary attempts on a catalytic enantioselective process has been performed using (*R,R*)-PhBPE giving product **474** (absolute configuration not reported) in only 11% yield and 92% ee by intermediacy of cyclopropylcopper **I** (Scheme 150).

alt-text: Scheme 150

Scheme 150

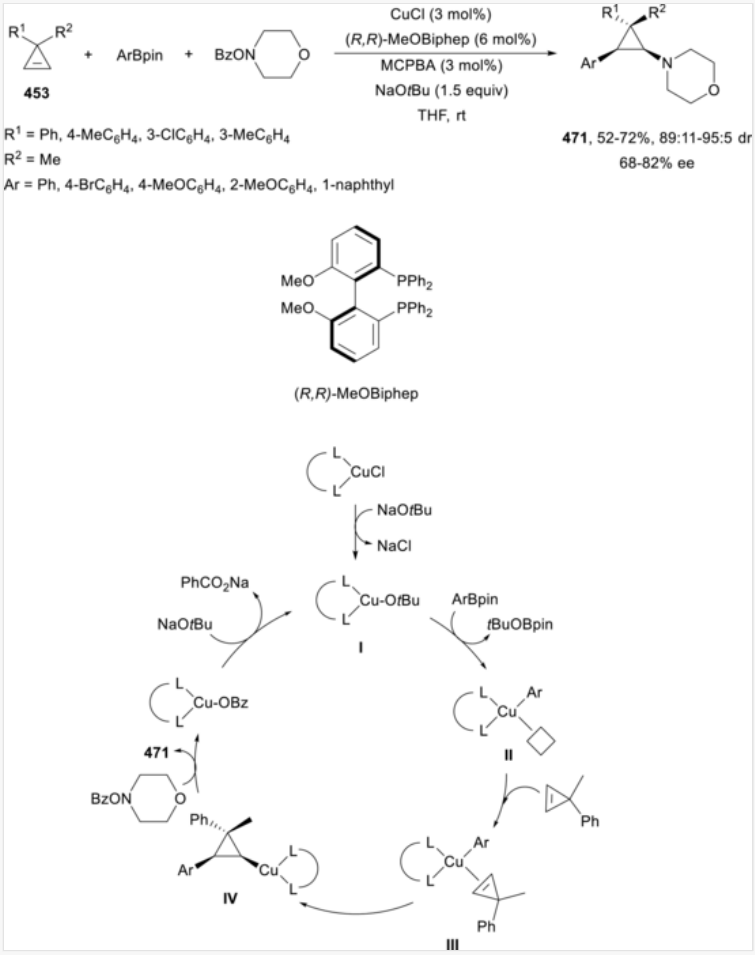


Cu-Catalyzed desymmetrization of cyclopropene **453** by an enantioselective dicarbofunctionalization with an arylboronate and allyl bromide.

The former multicomponent reaction has been applied to the enantioselective synthesis of polysubstituted 2-arylcyclopropylamines **471** by the Zhang's group [273]. In this case, arylboronic pinacolates and an *O*-benzoyl hydroxylamine were employed and different bis-phosphines as chiral ligands. By using (*R,R*)-MeO-Biphep, MCPBA as additive and NaO*t*Bu as base the corresponding products **471** were obtained in moderate to good yields, diastereo- and enantioselectivities (Scheme 151). According to experimental studies a plausible catalytic cycle was proposed. The reaction started by formation of copper alkoxide **I**, which by transmetalation with the arylboronic ester gives arylcopper **II**. Then, carbocupration of the cyclopropene **453** *via* a π-complex **III** affords stereoselectively cyclopropylcopper **IV**. Oxidative trapping of **IV** by the *O*-benzoyl hydroxylamine provides product **471** and CuOBz.

alt-text: Scheme 151

Scheme 151

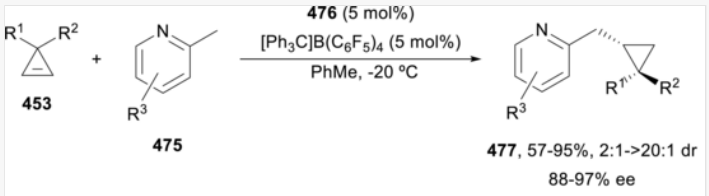


Cu-Catalyzed desymmetrization of cyclopropenes **453** by an enantioselective three-component carbometalation-amination.

Chiral half-sandwich rare-earth metal complexes **455–457** have been used in hydroamination of cyclopentenes by Hou and co-workers [260]. This type of catalysts have been employed for the asymmetric Csp^2–H addition of 2-methylazaarenes **475** to cyclopropenes **453** to give substituted cyclopropanes **477** (Scheme 152) [274]. The best results have been obtained with yttrium catalyst **476** in the presence of $[Ph_3C]B(C_6F_5)_4$ as co-catalyst at −20 °C in toluene. In the proposed mechanism a cationic yttrium alkyl species **I** deprotonates the 2,6-lutidine to form intermediate **II**. Then, coordination of cyclopropene takes place followed by insertion of the cyclopropene unit into the C–Y bond to provide **III**, which after deprotonation of other molecule of 2,6-lutidine affords the final product.

alt-text: Scheme 152

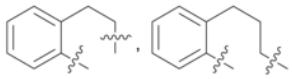
Scheme 152



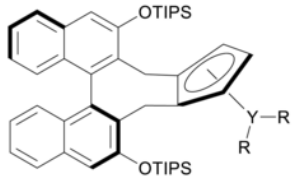
R^1 = 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-BrC_6H_4, 4-FC_6H_4, 3-ClC_6H_4, 2-ClC_6H_4, 2-thienyl, Ph, Bn

R^2 = Me, *i*Bu, Ph

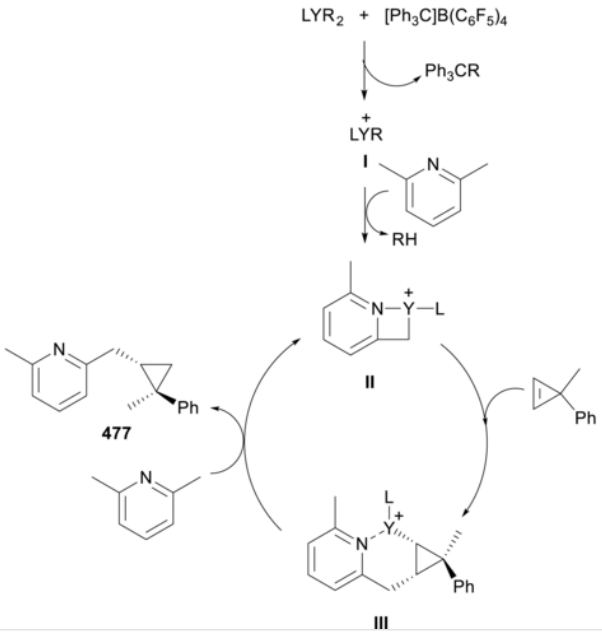
R^1-R^2 =



R^3 = 6-Me, 4,6-Me_2, 4-Br,6-Me, 4-*i*PrO,6-Me, 4-Me,6-*n*C_5H_{11}, 4-Me,6-CH_2=$CH(CH_2)_3$, 4-Me,4-$(Me_3Si)(CH_2)_3$, 4-Me,6-*i*Bu, 4-Me,6-$C_5H_9CH_2$, 4-Me,6-$C_6H_{11}CH_2$, 4-Me,6-$C_7H_{13}CH_2$, 5,6-benzo



476, R = $CH_2C_6H_4$-4-NMe_2

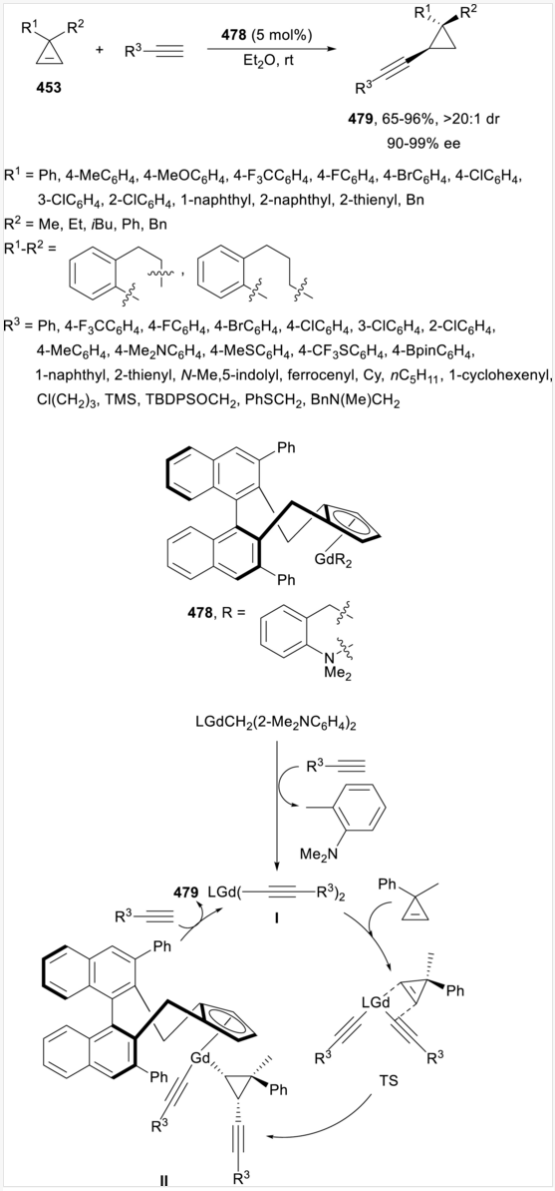


Y-Catalyzed desymmetrization of cyclopropenes **453** by an enantioselective Csp^2–H activation-addition of 2-methylazaarenes **475**.

Asymmetric Csp–H addition of terminal alkynes to cyclopropenes **453** using a chiral gadolinium catalyst **478** has been reported also by Hou's group [275]. This hydroalkynylation of cyclopropenes gave alkynylcyclopropanes **479** in high yields, diastereo- and enantioselectivities (Scheme 153). A possible catalytic cycle is depicted in Scheme 153. After the formation of the alkynylgadolinium species **I** and insertion *via* **TS**, the cyclopropyl species **II** can be formed. Protonation of **II** with the terminal alkyne gives product **479** and regenerates intermediate **I**.

alt-text: Scheme 153

Scheme 153

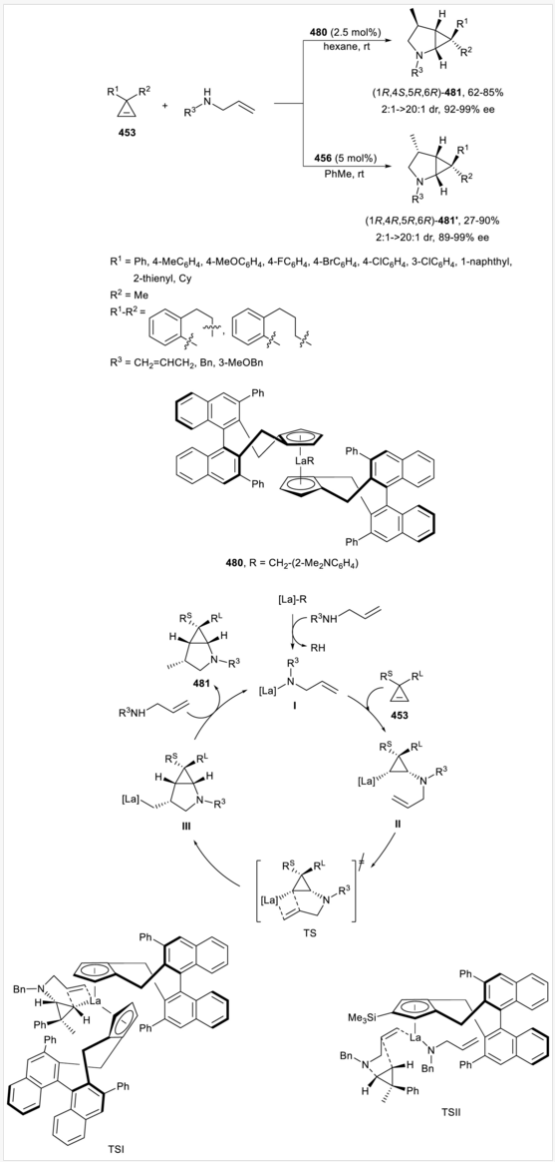


Gd-Catalyzed desymmetrization of cyclopropenes **453** by an enantioselective Csp–H addition of terminal alkynes.

Bicyclic aminocyclopropanes (1*R*,4*S*,5*R*,6*R*)-**481** have been prepared by Hou's group in a diastereo- and enantiodivergent manner by asymmetric carboamination/annulation of cyclopropenes **453** with allylamines using a chiral lanthanum catalyst **480** (Scheme 154) [276]. On the other hand, bicyclic aminocyclopropanes (1*R*,4*R*,5*R*,6*R*)-**481′** were obtained changing catalyst **480** by **456**. Both processes took place diastereodivergently [44] with high yields and stereoselectivities. A catalytic cycle was proposed for the first desymmetrization in which complex **480** reacts with the allylamine to provide the catalytic intermediate **I**. Then, by reaction with cyclopropene **453** a C═C aminometalation took place to give intermediate **II**, which after formation of **TS** the annulation step took place affording intermediate **III**. Final protonation of **III** by the allylamine gave product **481** and the catalytic species **I**. In order to explain the diastereodivergent results **TSI** and **TSII** have been proposed.

alt-text: Scheme 154

Scheme 154



La-Catalyzed desymmetrization of cyclopropenes **453** by an enantioselective carboamination/annulation with allylamines.

7.3 Cyclobutanes and cyclobutenes

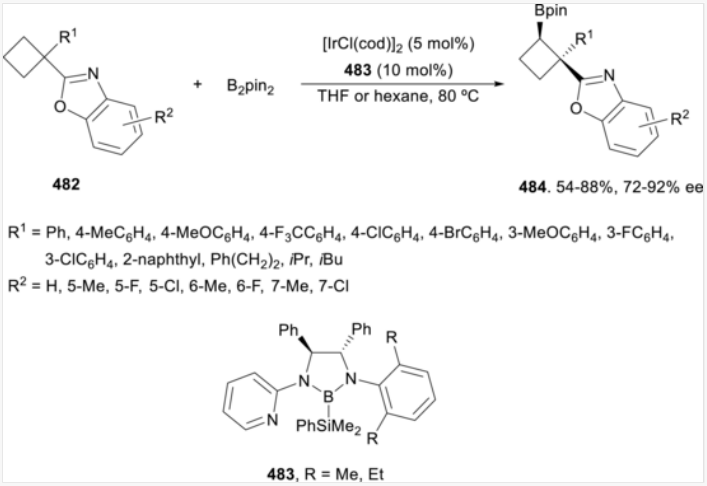
As in the case of cyclopropanes, chiral cyclobutanes are important structural motifs frequently found in bioactive compounds and natural products [277–279]. In this section, recent desymmetrizations of cyclobutanes, cyclobutanols, cyclobutanones and cyclobutenes will be considered.

Desymmetrization of cyclobutanecarboxylic acid derivatives has been performed by enantioselective Csp^3–H bond arylation with arylboronates under Pd-catalysis [254,280]. These processes are similar to the arylation of cyclopropanecarboxylic acids as it has been described in Scheme 138 [254]. Pd(II)-Catalyzed enantioselective Csp^3–H borylation has been reported also by Yu and co-workers for cyclopropyl and cyclobutyl carboxamides [251]. Indium-catalyzed enantioselective Csp^3–H borylation of cyclopropane carboxamides has been described by Shen, Xu and co-workers [252]. They recently reported that, as in the case of cyclopropane carboxamides **431** (Scheme 137) [252], cyclobutanes bearing a benzoxazoline unit **482** underwent enantioselective Csp^3–H borylation under Ir-catalysis using chiral bidentate boryl ligands **483** related to **432** (Scheme 155) [281]. This process took place with high yields and enantioselectivities giving cyclobutylboronates **484** by a similar mechanism described in Scheme 137. Both types of ligands **483** afforded similar results. Intermediate **I** determines the step of stereoselective oxidative addition of the

$C(sp^3)$–H bond in which the CH_2 group of the cyclobutane points to pyridine and phenyl groups of the catalyst present no repulsive interactions.

alt-text: Scheme 155

Scheme 155

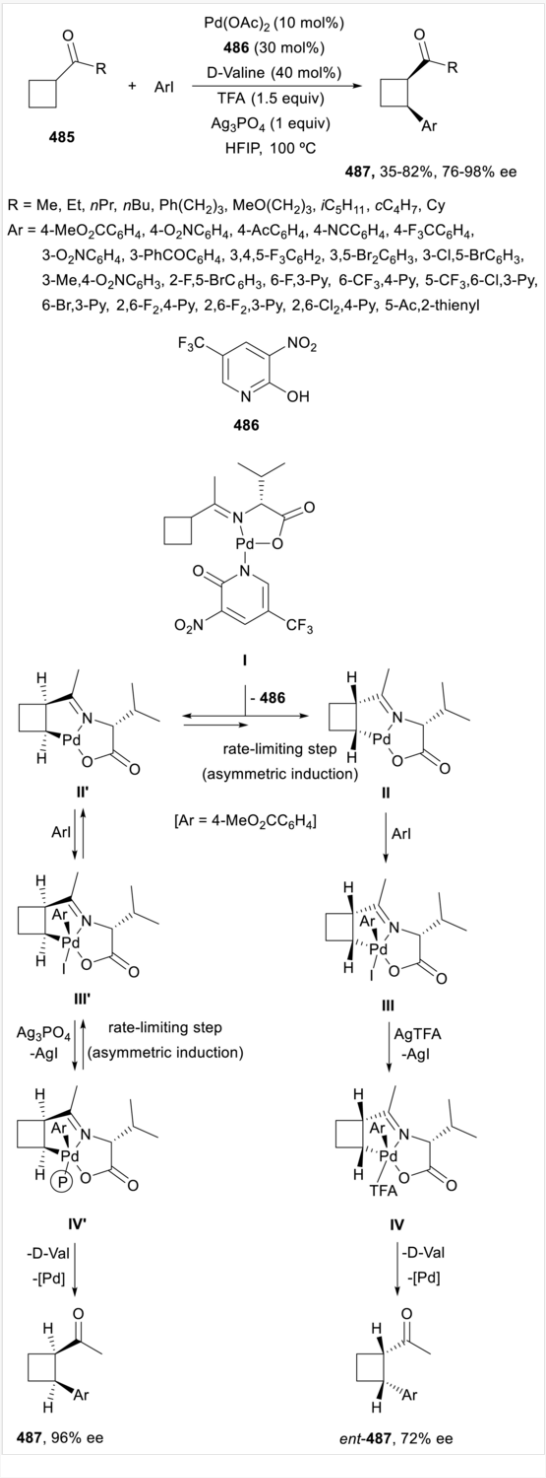


Ir-Catalyzed desymmetrization of cyclobutanes **482** by an enantioselective borylation.

Enantioselective Csp^3–H arylation of cyclobutyl ketones **485** with aryl iodides has been described by Yu and co-workers [282] This process occurred under Pd-catalysis using D-valine as transient directing group and 2-hydroxy-3-nitro-4-trifluoromethylpyridine (**486**) as ligand to provide products **487** with good yields and enantioselectivities (Scheme 156). The presence of a silver salt in stoichiometric amounts resulted crucial to control the rate-limiting steps, which leads to better results. In addition, when two different silver salts, AgTFA and Ag_3PO_4, are used as additives a reversal enantioselectivity [44] was observed. In the proposed mechanism the pyridone ligand accelerates the C–H bond cleavage step to form the palladacycles **II** and **II′** from complex **I**. After oxidative addition of the aryl iodide to palladacycles **II** and **II′** resulted the Pd(IV) complexes **III** and **III'**. Since AgTFA rapidly abstracts the iodide from the Pd(IV) intermediates **IV** to promote C–C reductive elimination, the initial C–H bond cleavage will be the rate-limiting step and the C–H palladation controls the enantioselectivity. In contrast, the rate-limiting step with $AgPO_4$ is the reductive elimination and the chiral Pd(IV) intermediate **IV'** is responsible for the asymmetric induction.

alt-text: Scheme 156

Scheme 156

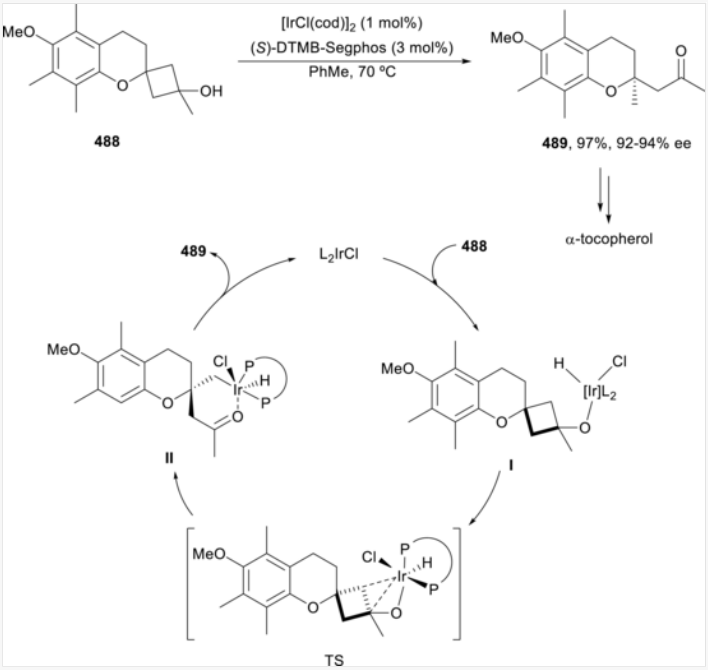


Pd-Catalyzed desymmetrization of cyclobutyl ketones **485** by an enantioselective arylation with aryl iodides.

Tertiary cyclobutanols can be enantioselectively desymmetrized under Pd and Rh catalysis to give acyclic or cyclic β-substituted ketones by a β-carbon elimination of intermediate cyclobutanolates [13]. Recently, Schmalz and co-workers [283,284] reported the total synthesis of α-tocopherol through enantioselective Ir-catalyzed fragmentation of a spiro-cyclobutanol **488**. Initial assays under Rh-catalysis and different chiral ligands following the protocol of Cramer [285] gave racemic **489**. However, using Ir-catalysis and (*S*)-DTBM-Segphos as a chiral ligand in toluene at 70 °C **489** was obtained in 97% yield and 92–94% ee (Scheme 157) [283]. This methodology has been applied to different spiro-cyclobutanols to provide the corresponding ketones in 47–99% yields and 18–95% ee [284]. From experimental and theoretical studies, they proposed the initial formation of an Ir(III) hydride intermediate **I** which through **TS** underwent a β-carbon elimination to give the Ir(III)-alkyl intermediate **II**. Final reductive elimination of **II** provided the corresponding ketone.

alt-text: Scheme 157

Scheme 157



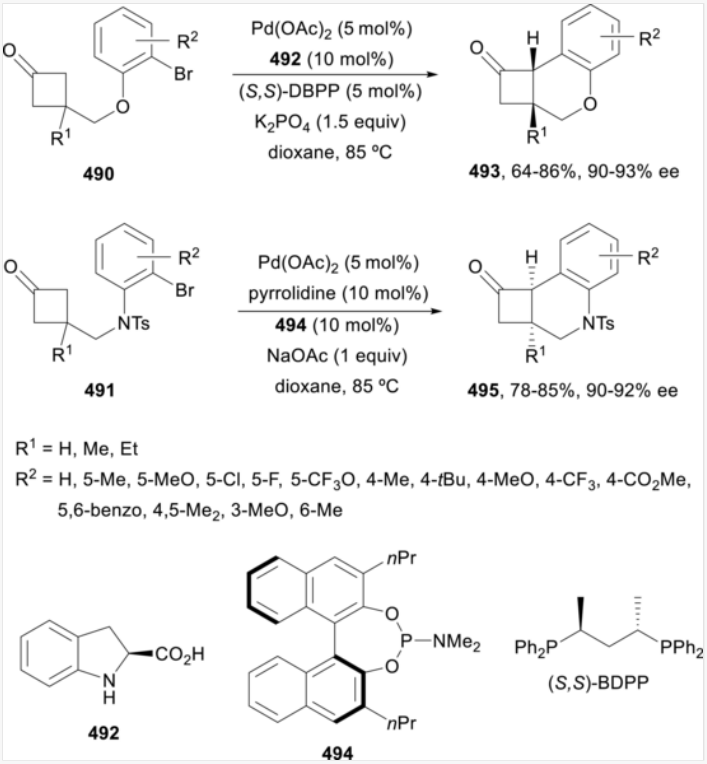
Ir-Catalyzed desymmetrization of spirocyclobutanol **488** by an enantioselective fragmentation.

Desymmetrization of 3,3-disubstituted cyclobutanones has been performed by transition metal-catalyzed ring-opening processes, intramolecular alkene insertions and carbonyl carboacylations mainly under Rh-catalysis [13]. Chiral phosphoric acid catalyzed Baeyer-Villiger oxidation gave the corresponding γ-lactones [286].

Recently, Lu and co-workers [287] described an intramolecular enantioselective desymmetrization of cyclobutanones **490** and **491** bearing an aryl bromide at the heteroatom. They used two different catalytic strategies, (*S*)-indoline-2-carboxylic acid **492** for the enamine formation of compounds **490** and (*S,S*)-BDPP derived Pd(II) complex for the intramolecular arylation to provide products **493** (Scheme 158). In the case of the *N*-tethered aryl bromide **491**, a chiral phosphoramidite **494** as ligand for Pd(II) and pyrrolidine as base were employed to give products **495** with up to 92% ee.

alt-text: Scheme 158

Scheme 158



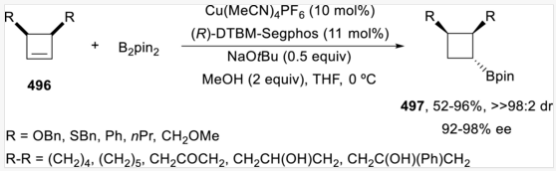
Pd and amine catalyzed desymmetrization of cyclobutanones **490** and **491** by an enantioselective intramolecular arylation.

Tortosa and co-workers have applied the copper-catalyzed enantioselective desymmetrization of cyclopropenes **453** [288] and cyclobutenes **496** [289] by a borylation reaction. In the presence of (*R*)-DTBM-Segphos as a chiral ligand, the borylation of *cis*-3,4-disubstituted cyclobutenes **496** with B_2pin_2 took place under mild conditions to give cyclobutylboronates **497** in good yields, total diastereoselectivity and high enantioselectivity (Scheme 159).

Images are optimised for fast web viewing. Click on the image to view the original version.

alt-text: Scheme 159

Scheme 159



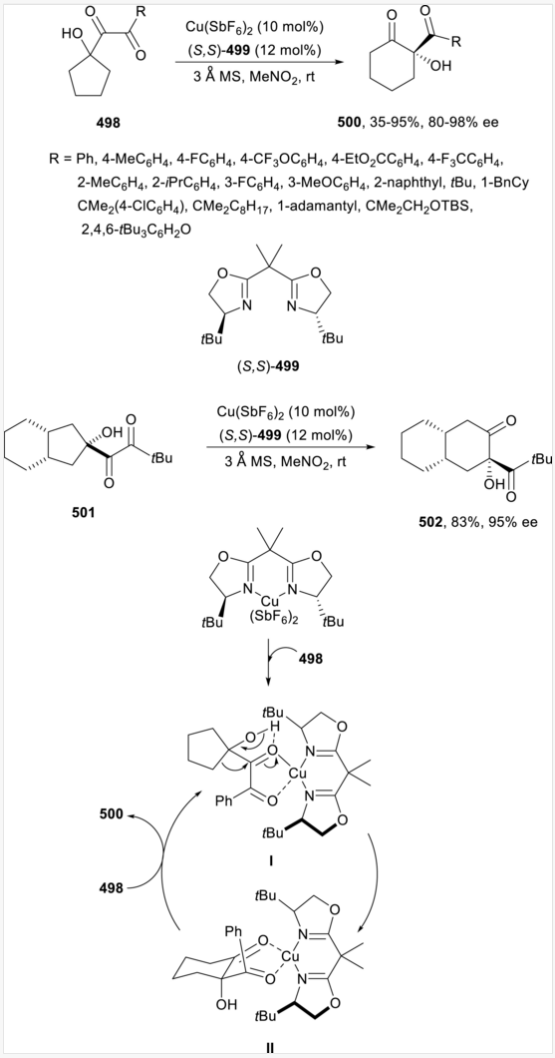
Cu-Catalyzed desymmetrization of cyclobutenes **496** by an enantioselective hydroborylation.

7.4 Cyclopentanes and cyclopentenes

Desymmetrization of five-membered ring carbocycles has been mainly carried out with cyclopentanol derivatives. One example about the enantioselective α-ketol rearrangement has been described by Zhu and co-workers [290] for desymmetrization of cyclopentanols **498**. In the presence of (*S,S*)-*t*BuBox (**499**) as a chiral ligand, the Cu-catalyzed isomerization of the five membered β-hydroxy-α-dicarbonyl compounds **498** gave chiral six-membered α-hydroxy-β-dicarbonyls **500** in good yields and enantioselectivities (Scheme 160). Desymmetrization of the cyclopentanol derived from octahydro-2*H*-inden-2-one **501** gave rearranged product **502**. In the proposed catalytic cycle, after coordination of starting compound **498** (R = Ph) with the catalyst complex **I** would be formed. Selective migration of the C–C bond to the *Si* face of the vicinal carbonyl group and proton transfer would furnish complex **II**, which upon ligand exchange with **498** (R = Ph) would generate product **500** (R = Ph).

alt-text: Scheme 160

Scheme 160

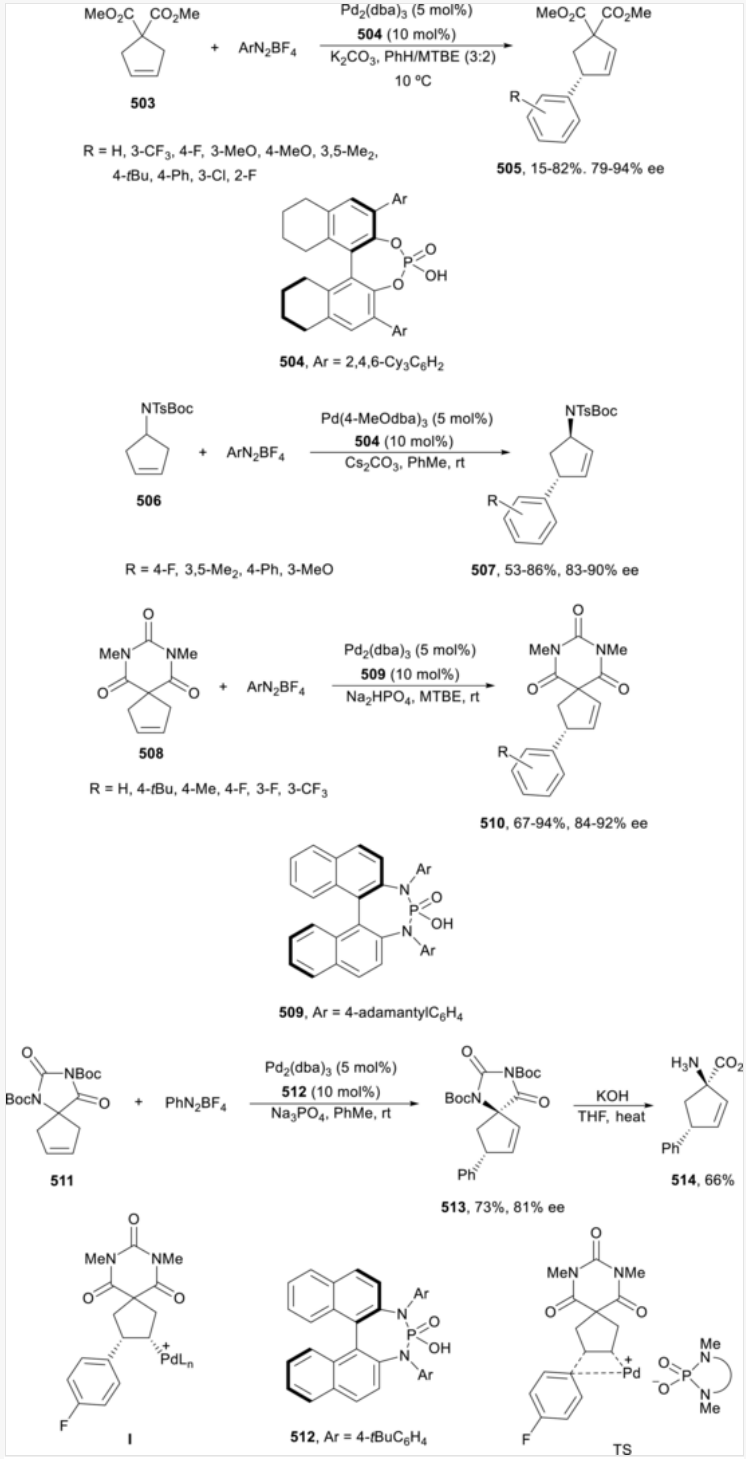


Cu-Catalyzed desymmetrization of cyclopentanols **498** and **501** by an enantioselective α-ketol rearrangement.

Different 4-functionalized cyclopentenes have been desymmetrized mainly by transition metal-catalyzed enantioselective arylations. Correia and co-workers [291] reported in 2012 the first example of the enantioselective Heck-Masuda reaction using chiral bisoxazolines as ligands for the desymmetrization of 4,4-bis(methoxycarbonyl)cyclopentene (**503**) and also the monoester using aryldiazonium salts with up to 84% ee. Sunoj, Toste and co-workers [292] performed in 2017 the same arylative desymmetrization of diester **503** using the chiral anion of phosphoric acid **504** as co-catalyst of Pd(0). The corresponding products **505** were obtained in good yields and enantioselectivities (Scheme 161). These chiral anion phase-transfer conditions were also applied to *N*-Boc protected *N*-tosylcyclopentenylamine **506** to provide *trans*-derivatives **507**. In the case of spirocyclic substrates **508**, the binaphthyldiamine (BINAM) derived phosphoric acid **509** gave products **510** with the best enantioselectivities. This methodology was applied to the synthesis of constrained amino acid **514** by arylation of hydantoin derivative **511** using the phosphoric acid **512** to give product **513** with 73% yield and 81% ee. Recent DFT calculations for the reaction of **508** with 4-fluorophenyl diazonium tetrafluoroborate using phosphoric acid **509** have been carried out by the same groups [293]. They found out that the oxidative addition of Pd(0) to the aryldiazonium bond gives rise to a Pd-aryl intermediate, which by enantioselective migratory insertion to the cyclic alkene **508** leads to an arylated cycloalkane **I** through the **TS**. Final β-hydride elimination on complex **I** provides product **510**.

alt-text: Scheme 161

Scheme 161

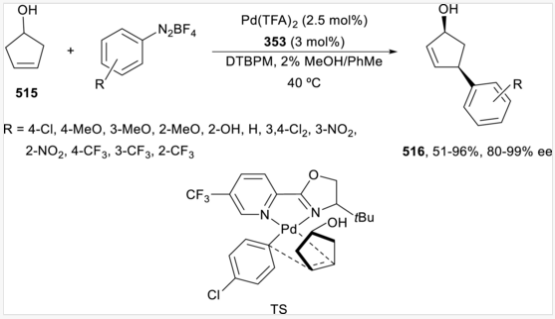

MeO2C CO2Me
503
+ ArN2BF4
Pd2(dba)3 (5 mol%)
504 (10 mol%)
K2CO3, PhH/MTBE (3:2)
10 ºC
MeO2C CO2Me
R
R = H, 3-CF3, 4-F, 3-MeO, 4-MeO, 3,5-Me2, 4-tBu, 4-Ph, 3-Cl, 2-F
505, 15-82%. 79-94% ee
Ar
O
P
O
OH
O
Ar
504, Ar = 2,4,6-Cy3C6H2
NTsBoc
506
+ ArN2BF4
Pd(4-MeOdba)3 (5 mol%)
504 (10 mol%)
Cs2CO3, PhMe, rt
NTsBoc
R
R = 4-F, 3,5-Me2, 4-Ph, 3-MeO
507, 53-86%, 83-90% ee
O
MeN
NMe
O
O
508
+ ArN2BF4
Pd2(dba)3 (5 mol%)
509 (10 mol%)
Na2HPO4, MTBE, rt
MeN
NMe
R
R = H, 4-tBu, 4-Me, 4-F, 3-F, 3-CF3
510, 67-94%, 84-92% ee
Ar
N
P
O
OH
N
Ar
509, Ar = 4-adamantylC6H4
NBoc
BocN
O
511
+ PhN2BF4
Pd2(dba)3 (5 mol%)
512 (10 mol%)
Na3PO4, PhMe, rt
NBoc
BocN
Ph
KOH
THF, heat
H3N CO2
Ph
513, 73%, 81% ee
514, 66%
MeN
NMe
PdLn
F
I
512, Ar = 4-tBuC6H4
Pd
Me
N
O
P
O
N
Me
F
TS

Pd-Catalyzed desymmetrization of cyclopentene derivatives **503**, **506**, **508** and **511** by an enantioselective Heck-Matsuda arylation.

When cyclopentenol **515** was submitted to enantioselective Heck-Matsuda arylative desymmetrization using the bisoxazoline **353** (R = 5-CF_3) as a chiral ligand and 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) as base the corresponding 4-arylcyclopentenols **516** were obtained together with some 3-arylcyclopentanones [294]. Further theoretical studies by DFT calculations provided better reaction conditions to achieve higher chemo- and enantioselectivities (Scheme 162) [295]. Similar results were obtained using ligand **353** with R = 3,5-Cl_2 as substituents. According to these calculations **TS** which has the hydroxyl in an *endo* orientation toward Pd is the less energetic.

alt-text: Scheme 162

Scheme 162

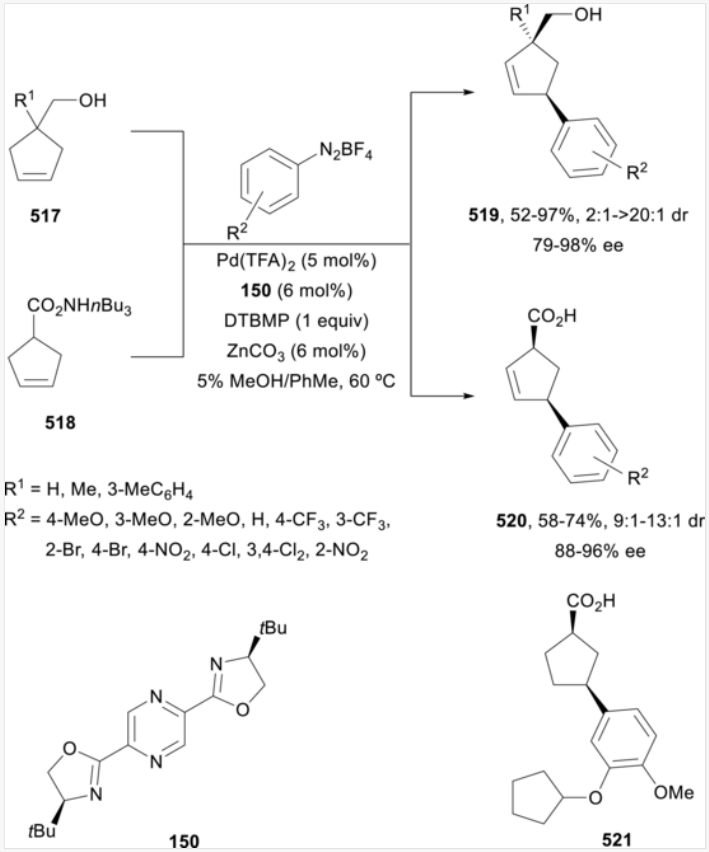


Pd-Catalyzed desymmetrization of cyclopentenol **515** by an enantioselective Heck-Matsuda arylation.

Correia and co-workers [296] applied the former desymmetrization to different cyclopentenyl derivatives containing hydroxymethyl **517** and carboxylate **518** functional groups (Scheme 163). The corresponding *cis*-arylated products **519** and **520** were obtained in good yields, diastereo- and enantioselectivities using Pyrabox (**150**) as a chiral ligand. In addition, oxidative Heck reactions using arylboronic acids gave similar results. The Heck-Matsuda process was applied to the straightforward synthesis of the potent phosphodiesterase inhibitor **521**. DFT calculations supported the stabilized internal out-of-coordination-sphere ion-dipole interaction between the functional group and cationic palladium in **TS**.

alt-text: Scheme 163

Scheme 163

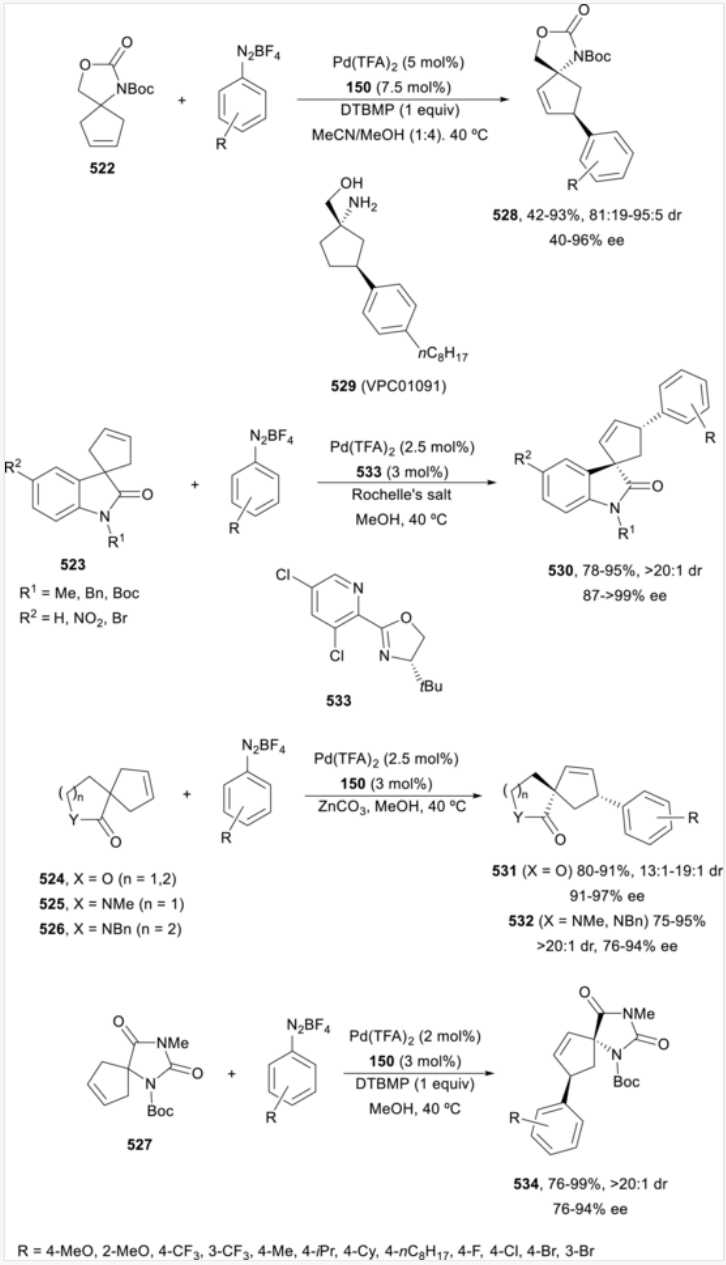


Pd-Catalyzed desymmetrization of cyclopentenyl methanols **517** and carboxylate **518** by an enantioselective Heck-Matsuda arylation.

The same group has applied the Heck-Matsuda desymmetrization to spirocyclopentenyl derivatives such as spiropyrrolidinone **522** [297], spirooxindoles **523** [298], spirolactones **524** [298], spirolactams **525** and **526** [298] and spirohydantoin **527** [299] (Scheme 164). In the case of compound **522**, Pyrabox (**150**) was used as a chiral ligand giving products **528** in good yields and stereoselectivities [297]. The authors propose **TSI** to explain the stereochemical outcome in which the coordination to the cyclopentenyl substrate is at the opposite face respect to the Boc group. This process was applied to the total synthesis of the highly selective sphingosine-1-receptor VPC01091 (**529**). Spirooxindoles **523**, lactones **524** and lactams **525** and **526** provided the corresponding products **530**, **531** and **532**, respectively, using ligand **533** and Pyrabox (**150**) in the case of **531** and **532** [298]. In the case of **530**, **TSII** has been proposed, in which the carbonyl group directs the approaching of **523** to the catalyst. Spirohydantoin **527** underwent Heck-Matsuda arylations in the presence of Pyrabox (**150**) affording products **534** with high yields and total diastereoselectivities [299]. The stereochemistry of compounds **532** and **534** are explained by **TSIII** and **IV**, respectively, in which a covalent interaction of the carbonyl group directs the approaching of the starting compounds. This last procedure was also applied to the total synthesis of VPC01091 (**529**).

alt-text: Scheme 164

Scheme 164

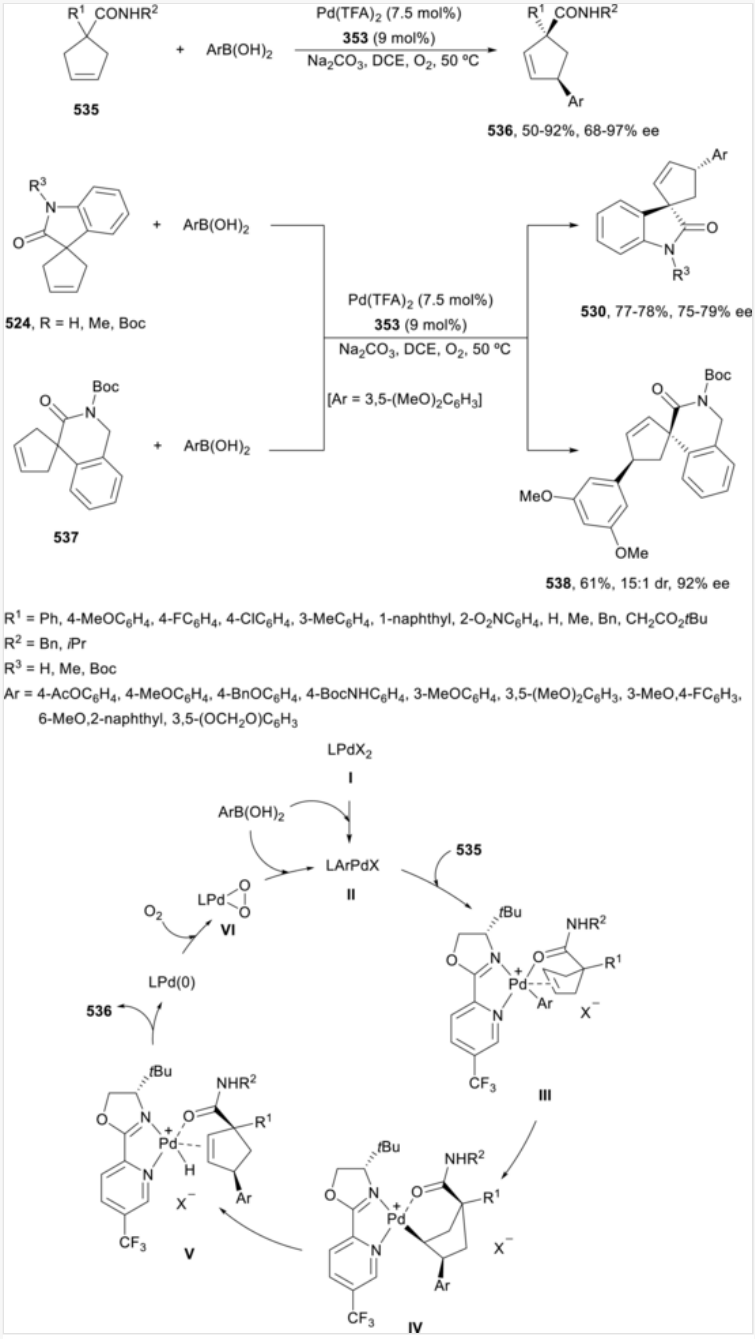


Pd-Catalyzed desymmetrization of spiro compounds **522–527** by an enantioselective Heck-Matsuda arylation.

Recently, Zhu and co-workers [300] reported the desymmetrization of cyclopentenecarboxamides **535** by enantioselective Pd-catalyzed oxidative Heck reaction (Scheme 165). They used Pyox **353** (R = 5-CF_3) as a chiral ligand to provide products **536** by arylation with arylboronic acids under oxygen atmosphere. This process has been applied to spirocyclopentenes **524** and **537** which afforded the arylated spiroindolin-2-ones **530** and a spirodihydroisoquinolin-3-one **538**, respectively, in good yields and stereoselectivities. A possible catalytic cycle has been proposed to explain the 1,4-*cis* relationship between the aryl and the carboxamides group. The Pd-complex **I** is formed firstly and then its transmetalation with an arylboronic acid would afford species **II**. Coordination of **II** with cyclopentene **535** directed by the amide functionality would generate a pentacoordinate Pd complex **III** in which steric repulsion was minimized. After *syn*-carbopalladation of **III**, complex **IV** would be formed, which after β-hydride elimination giving complex **V** would generate product **536** and a Pd(0) species. Oxidation of Pd(0) by oxygen to Pd(II)-peroxo complex **VI** followed by reaction with arylboronic acid would afford species **II**.

alt-text: Scheme 165

Scheme 165



R^1 = Ph, 4-$MeOC_6H_4$, 4-FC_6H_4, 4-ClC_6H_4, 3-MeC_6H_4, 1-naphthyl, 2-$O_2NC_6H_4$, H, Me, Bn, CH_2CO_2tBu

R^2 = Bn, *i*Pr

R^3 = H, Me, Boc

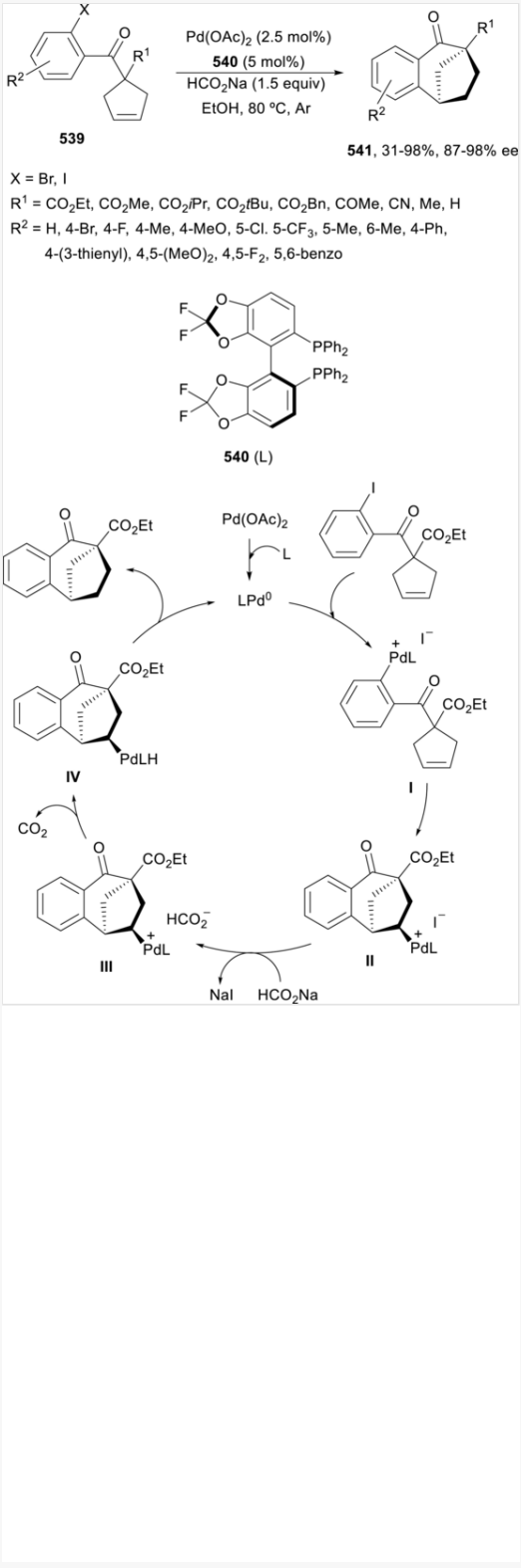
Ar = 4-$AcOC_6H_4$, 4-$MeOC_6H_4$, 4-$BnOC_6H_4$, 4-$BocNHC_6H_4$, 3-$MeOC_6H_4$, 3,5-$(MeO)_2C_6H_3$, 3-MeO,4-FC_6H_3, 6-MeO,2-naphthyl, 3,5-$(OCH_2O)C_6H_3$

Pd-Catalyzed desymmetrization of cyclopentenyl derivatives **535**, **524** and **357** by an enantioselective oxidative Heck arylation.

Liu, Yao and co-workers [301] have described desymmetrization of disubstituted cyclopentenes **539** by an asymmetric intramolecular reductive Heck reaction. This process gave access to bicyclo[3.2.1]octanes **541** with up to 98% yield and up to 98% ee using (*S*)-Difluorphos (**540**) as bidentate chiral ligand and sodium formate as hydride donor (Scheme 166). In the proposed mechanism the substrate **539** undergoes oxidative addition of the Pd catalyst to provide complex **I**. Next, intramolecular *syn*-migratory insertion of **I** leads to intermediate **II**, which by anion exchange with HCO_2Na delivers intermediate **III**. This palladium complex **III** converts into the hydropalladium species **IV** by releasing of CO_2. Final reductive elimination of **IV** gives rise to product **541**.

alt-text: Scheme 166

Scheme 166

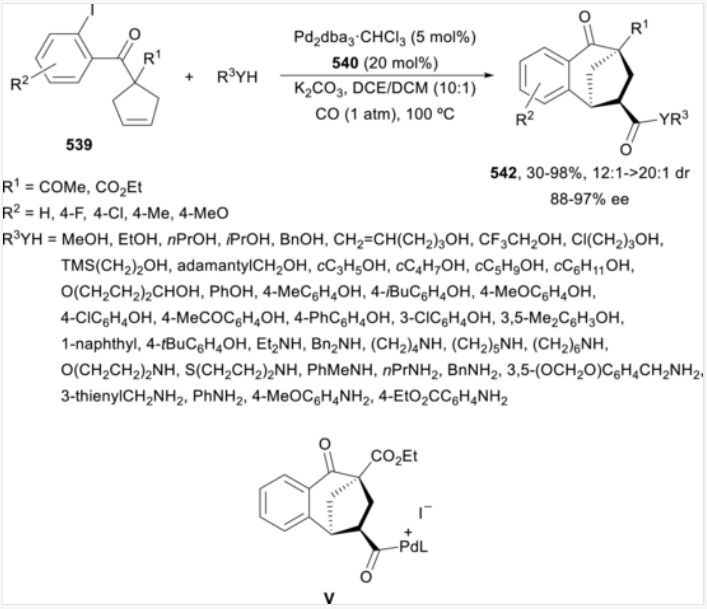


Pd-Catalyzed desymmetrization of cyclopentenes **539** by an enantioselective intramolecular reductive Heck reaction.

The same group [302] reported the construction of chiral bicyclo[3.2.1]octanes **542** by a Pd-catalyzed tandem Heck/carbonylation reactions of cyclopentenes **539** (Scheme 167). This desymmetrization was carried out in the presence of alcohols, phenols and amines giving compounds **542** using (*S*)-Difluorphos (**540**) as a chiral ligand. In this case, intermediate **II** (Scheme 166) underwent CO insertion to give intermediate **V**, which after nucleophilic insertion of the alcohol produces the product **542**.

alt-text: Scheme 167

Scheme 167



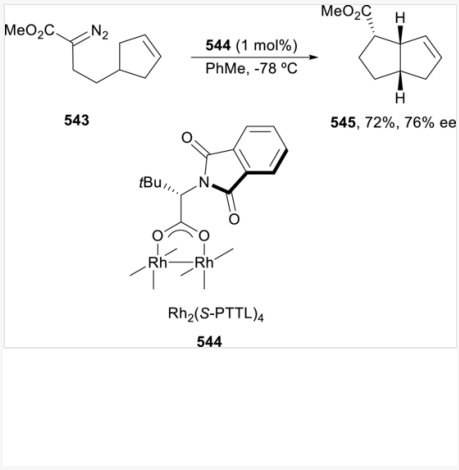
Pd-Catalyzed desymmetrization of cyclopentenes **539** by an enantioselective tandem intramolecular Heck reaction/carbonylation/nucleophile insertion.

Fused bicyclic ring systems have been prepared by an enantio- and diastereoselective intramolecular C–H insertion including a α-alkyl-α-diazoester **543** tethered to cyclopentene [303] (Scheme 168). This desymmetrization process was carried out using chiral dirhodium(II) tetrakis[*N*-phthaloyl-(*S*)-*tert*-leucinate], Rh_2(*S*-PTTL)$_4$ (**544**) as catalyst. Methyl bicyclo[3.3.0]oct-7-ene-2-carboxylate **545** was obtained as *cis*-diastereomer with 76% ee. By comparing **TSI** and **TSII**, in which the Rh bound carbene inserts into the equatorial bond, the first **TSI** is preferred because in **TSII** there is severe steric repulsion between the cyclohexyl moiety and the dirhodium(II) framework. Compound **545** has been employed as key intermediate for the synthesis of natural udoteatrial hydrate.

Images are optimised for fast web viewing. Click on the image to view the original version.

alt-text: Scheme 168

Scheme 168



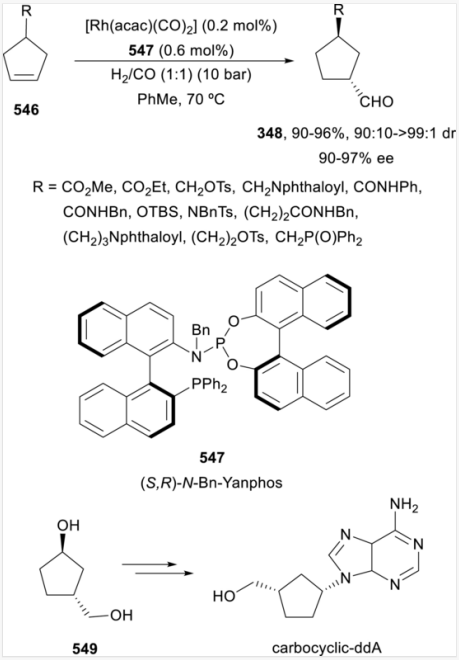
Rh-Catalyzed desymmetrization of α-alkyl-α-diazoester **543** by an enantioselective intramolecular C–H insertion.

The rhodium-catalyzed hydroformylation of cyclopropenes **453** [304] has been applied to desymmetrization of cyclopentenes [305]. Chiral *trans*-cyclopentanecarbaldehydes **548** were obtained by hydroformylation of cyclopentenes **546** using (*S,R*)-*N*-Bn-Yanphos (**547**) as chiral bidentate ligand (Scheme 169). The synthetic utility of this methodology was applied to the preparation of cyclopentanol **549**, a key intermediate for the synthesis of carbocyclic-ddA, by hydroformylation of *O*-TBS cyclopentenol.

Images are optimised for fast web viewing. Click on the image to view the original version.

alt-text: Scheme 169

Scheme 169



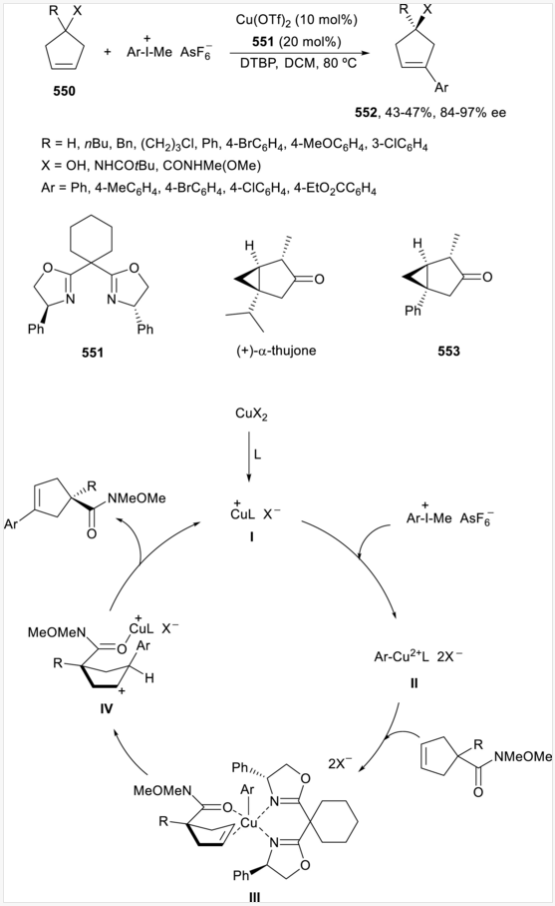
Rh-Catalyzed desymmetrization of functionalized cyclopentenes **546** by an enantioselective hydroformylation.

Zhu and co-workers [306] reported a copper-catalyzed arylation of cyclopentenes **550** with diaryliodonium salts in the presence of 2,6-di-*tert*-butylpyridine (DTBP). A chiral bisoxazoline **551** was used as ligand for desymmetrization of 4-substituted and 4,4-disubstituted cyclopentenes **550** to provide the arylated derivatives **552** in good yields and enantioselectivities (Scheme 170). In the proposed mechanism, oxidative addition of diaryliodonium salt to the Cu(I) species **I** formed the ArCu(II) intermediate **II**, which upon coordination to the cyclopentene **550** generates complex **III**. Next, electrophilic arylation of the double bond takes place forming the carbenium intermediate **IV**. Final removal of the benzylic hydrogen atom regenerates the double bond to provide the product. This method has been applied to the synthesis of an analogue **553** of thujone, an inhibitor of the γ-aminobutyric acid A (GABAA) receptor.

Images are optimised for fast web viewing. Click on the image to view the original version.

alt-text: Scheme 170

Scheme 170

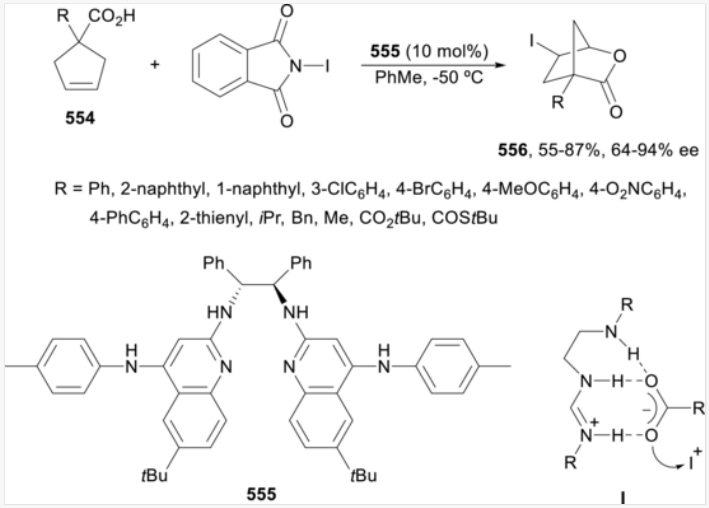


Cu-Catalyzed desymmetrization of cyclopentenes **550** by an enantioselective arylation with diaryliodonium salts.

Enantioselective iodolactonization of cyclopentenecarboxylic acids **554** using a chiral Brønsted base **555** as catalyst has been described by Johnston and co-workers [307]. The resulting bridged lactones **556** were obtained with up to 94% ee using *N*-iodophthalimide (Scheme 171). Crystallographic analysis of a substrate-catalyst complex revealed three hydrogen bonds that desymmetrizes the bound carboxylate and the attack of the I^+ is represented in a simplified structure **I**.

alt-text: Scheme 171

Scheme 171



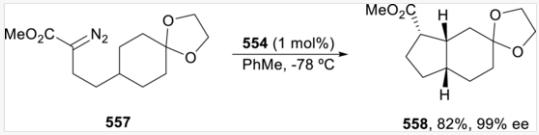
Brønsted base-organocatalyzed desymmetrization of cyclopentenecarboxylic acids **554** by an enantioselective iodolactonization.

7.5 Cyclohexanes, cyclohexenes and cyclohexadienes

Monosubstituted cyclohexanes bearing a tethered α-diazocarbonyl group have been desymmetrized by Rh-catalyzed intramolecular C−H insertion. Recently, Anada and co-workers [303] reported the desymmetrization of methyl-2-diazo-4-(1,4-dioxaspiro[4.5]decan-8-yl)butanoate (**557**) under the same reaction conditions than the cyclopentene derivative **543** in Scheme 168. The Rh_2(*S*-PTTL)$_4$ (**544**) was used as chiral catalyst to afford the *cis*-fused five-membered carbocycle **558** with 99% ee (Scheme 172).

alt-text: Scheme 172

Scheme 172

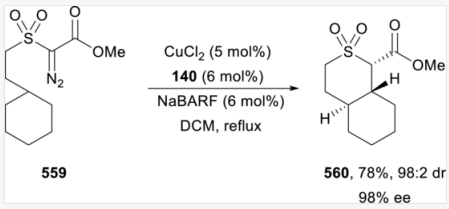


Rh-Catalyzed desymmetrization of cyclohexane **557** by an enantioselective intramolecular C–H insertion.

Maguire and co-workers [308] performed a similar cyclohexane derivatives **559** desymmetrization under Cu-catalyzed intramolecular C−H insertion. In this case α-diazo-β-oxosulfone **559** gave using $CuCl_2$, phenylbisoxazoline Phbox (**140**) and sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate (NaBARF) as catalyst complex system gave thiopyrane dioxide **560** as the major diastereomer with 98:2 dr and 98% ee (Scheme 173). However, this desymmetrization with a similar cyclopentane derivative proceeded with only 64% ee.

alt-text: Scheme 173

Scheme 173

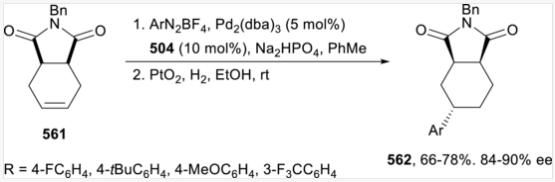


Cu-Catalyzed desymmetrization of cyclohexane **559** by an enantioselective intramolecular C−H insertion.

The enantioselective Heck-Matsuda arylation through chiral anion-phase transfer developed for cyclopentene derivatives **503**, **506**, **508** and **511** (Scheme 161) was also applied to the desymmetrization of cyclohexene **561** [292]. The reaction of **561** with aryldiazonium salts under Pd catalysis using the anion of phosphoric acid **504** gave products **562** after hydrogenation in good yields and enantioselectivities (Scheme 174).

alt-text: Scheme 174

Scheme 174

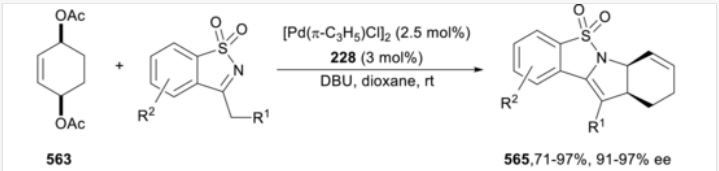


Pd-Catalyzed desymmetrization of cyclohexene **561** by an enantioselective Heck-Matsuda arylation.

Desymmetrization of *cis*-cyclohex-2-ene-1,4-diyl diacetate **563** [309] and dicarbonate **564** [310] has been carried out using Pd-catalyzed allylic substitution cascades. *N*-Sulfonylimines reacted with diacetate **563** using RuPhox (**228**) as a chiral ligand to provide fused tetrahydroindole derivatives **565** with 91–97% ee (Scheme 175). On the other hand, the Pd-RuPhox catalyzed asymmetric allylic substitution with 3-oxonitriles afforded bicyclic dihydrofurans **566** with high yields and enantioselectivities. In the proposed mechanistic cycle [309], first takes place the formation of the allyl-Pd complex **I** from diacetate **563**. Complex **I** then reacts with the nucleophile to give intermediate **II**, which gave the π-allyl-Pd complex **III**. Finally allylic intramolecular amination provides the heterocycle **565** and the original catalyst. The same group has recently carried out the desymmetrization of diacetate **563** with ketimines as nucleophiles [311]. Tetrahydroindoles **567** resulted by the Pd-catalyzed asymmetric allylic substitution (AAS) cascade in good yields and with up to 96% ee (Scheme 175). All these processes have been also carried out with *cis*-cyclopent-2-ene-1,4-diyl and cyclopent-2-ene-1,4-diyl derivatives [309–311].

alt-text: Scheme 175

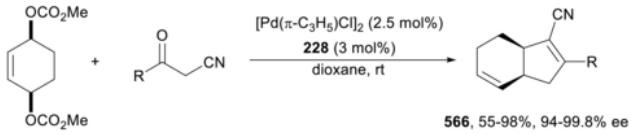
Scheme 175



563 **565**,71-97%, 91-97% ee

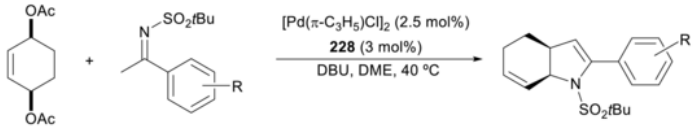
R^1 = Ph, 2-FC_6H_4, 3-FC_6H_4, 4-FC_6H_4, 2-BrC_6H_4, 4-BrC_6H_4, 4-ClC_6H_4, 4-$CF_3OC_6H_4$, 3,4-$F_2C_6H_3$, 2-MeC_6H_4, 3-MeC_6H_4, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-*t*BuC_6H_4, 2-naphthyl, Me, Et, Bn

R^2 = H, 5-Me, 5-*t*Bu



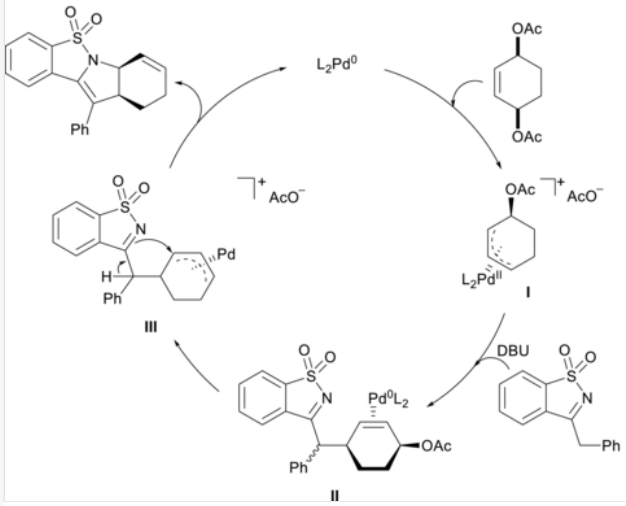
564 **566**, 55-98%, 94-99.8% ee

R = Ph, 2-MeC_6H_4, 3-MeC_6H_4, 4-MeC_6H_4, 3-$MeOC_6H_4$, 4-$MeOC_6H_4$, 4-*t*BuC_6H_4, 4-$CF_3OC_6H_4$, 2-FC_6H_4, 3-FC_6H_4, 4-FC_6H_4, 3-ClC_6H_4, 4-ClC_6H_4, 3-$F_3CC_6H_4$, 4-$F_3CC_6H_4$, 2,4-$Cl_2C_6H_3$, 3,4-$F_2C_6H_3$, 1-naphthyl, 2-naphthyl, 2-Py, 3-furyl, 3-thienyl, *c*C_3H_5, Et, $Ph(CH_2)_2$



563 **567**, 55-89%, 89-96% ee

R = Ph, 2-MeC_6H_4, 3-MeC_6H_4, 4-MeC_6H_4, 4-PhC_6H_4, 4-$F_3CC_6H_4$, 2-FC_6H_4, 3-FC_6H_4, 4-FC_6H_4, 3,4-$F_2C_6H_3$, 3-ClC_6H_4, 4-ClC_6H_4, 4-$F_3CC_6H_4$, 1-naphthyl, 2-naphthyl, 2-Py, 3-Py, 4-Py, 2-furyl

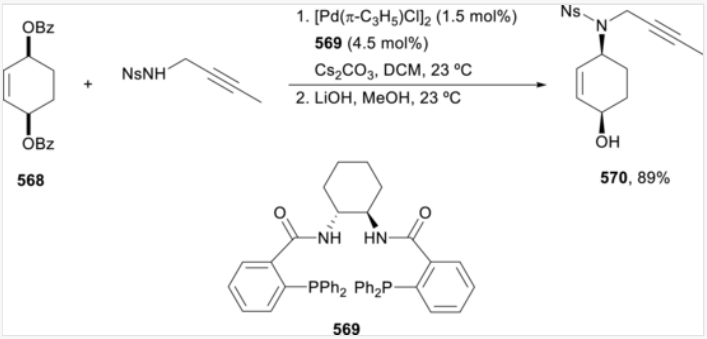


Pd-Catalyzed desymmetrization of *cis*-cyclohex-2-ene-1,4-diyl diacetate **563** and dicarbonate **564** by an enantioselective allylic substitution cascade.

Garg and co-workers [312] have reported the enantioselective total synthesis of methanoquinolizidine-containing alkuammiline alkaloids, an important family of bioactive natural products. The synthesis starts with the desymmetrization of *cis*-cyclohex-2-en-1,4-diyl benzoate (**568**) by AAS with a propargylic sulfonamide to afford product **570** (Scheme 176). In this case (*R,R*)-DACH-phenyl Trost ligand **569** was the suitable chiral ligand for the AAS.

alt-text: Scheme 176

Scheme 176

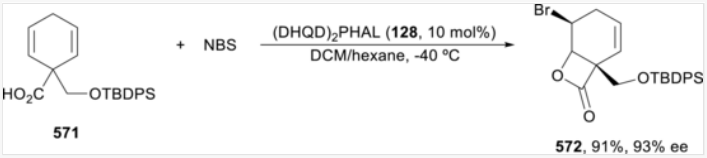


Pd-Catalyzed desymmetrization of *cis*-cyclohex-2-en-1,4-diyl benzoate (**568**) by an enantioselective allylic substitution.

Kan and co-workers [313] reported the total synthesis of SB-203207 and sphingofungin based on a desymmetrization strategy. Organocatalyzed bromolactonization of cyclohexa-1,4-dienecarboxylic acid derivative **571** with NBS and $(DHQD)_2PHAL$ (**128**) gave the key product **572** in 91% yield and 93% ee (Scheme 177).

alt-text: Scheme 177

Scheme 177



Organocatalyzed desymmetrization of cyclohexadiene **571** by an enantioselective bromolactonization.

8 Desymmetrization of saturated heterocycles

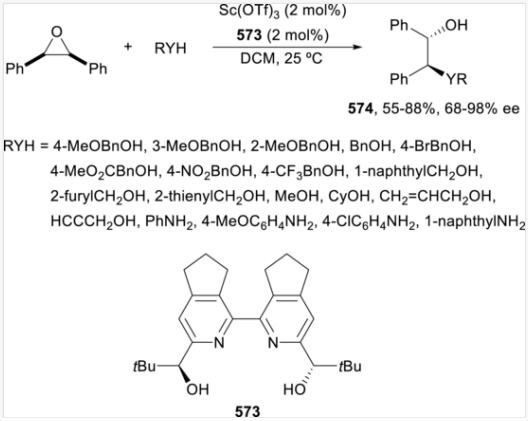
In this section desymmetrization of small-ring heterocycles, such as oxygen-containing epoxides, oxetanes and oxabenzonorbornadienes, as well as nitrogen-containing aziridines, azetidines, azabenzonorbornadienes and diazonorbornenes using metal-catalyzed and organocatalyzed processes will be presented.

8.1 Epoxides

Desymmetrization of *meso*-epoxides has been widely studied using asymmetric metal-catalyzed processes, organocatalyzed and enzymatic processes. In the case of metal-catalyzed methods several recent revisions have been published. Titanocene-catalyzed reductive epoxide opening by electron transfer reactions has been compiled by Gansäuer and co-workers [314]. Metal-salen complexes are privileged catalysts for the asymmetric ring opening of epoxides by nucleophiles [315] as well as different metal complexes with 2,2′-bipyridines called Bolm's ligands [316]. Concerning this last strategy, Kotora and co-workers [317] have recently published the ring opening of acyclic and cyclic *meso*-epoxides catalyzed by a Sc complex formed by $Sc(OTf)_3$ and the bipyridine ligand **573** with alcohols and aromatic amines (Scheme 178). These processes took place at room temperature to give products **574** with good yields and enantioselectivities.

alt-text: Scheme 178

Scheme 178

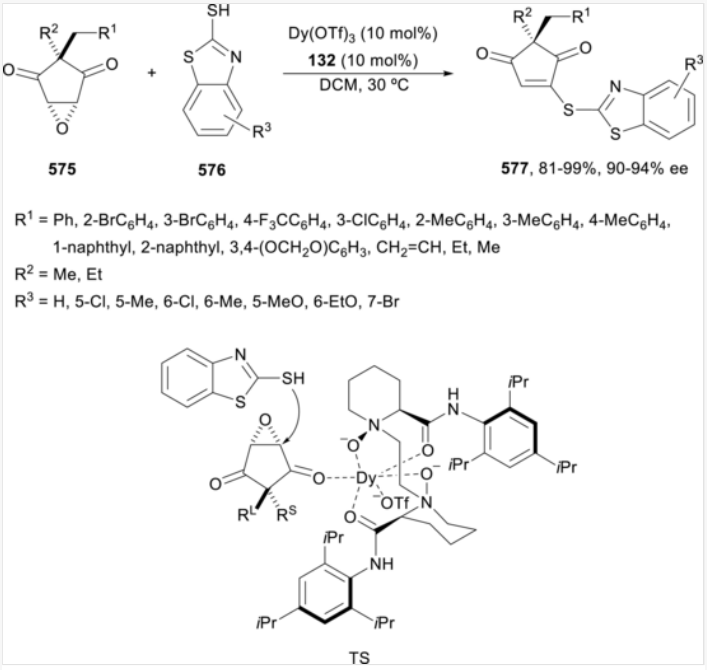


Sc-Catalyzed desymmetrization of *cis*-1,2-diphenyloxirane by an enantioselective ring opening with heteronucleophiles.

Instead of scandium(III) triflate, dysprosium(III) triflate and *N,N′*-dioxide **132** as a chiral ligand was used as catalyst for the desymmetrization of *meso*-epoxides **575** derived from cyclopentene-1,3-diones with 2-mercaptobenzothiazoles **576** (Scheme 179) [318]. The corresponding products **577** were formed through a thiolysis/elimination sequence with high yields and enantioselectivities. A possible favored **TS** has been proposed in which Dy(III) center gives rise to an active octahedral complex. The coordination of one of the carbonyls of the epoxide **575** with Dy(III) leads to lower electron density at the carbon atom of the epoxide and allows the nucleophilic attack of **576** from the backside to afford **577** with (*R*)-configuration.

alt-text: Scheme 179

Scheme 179

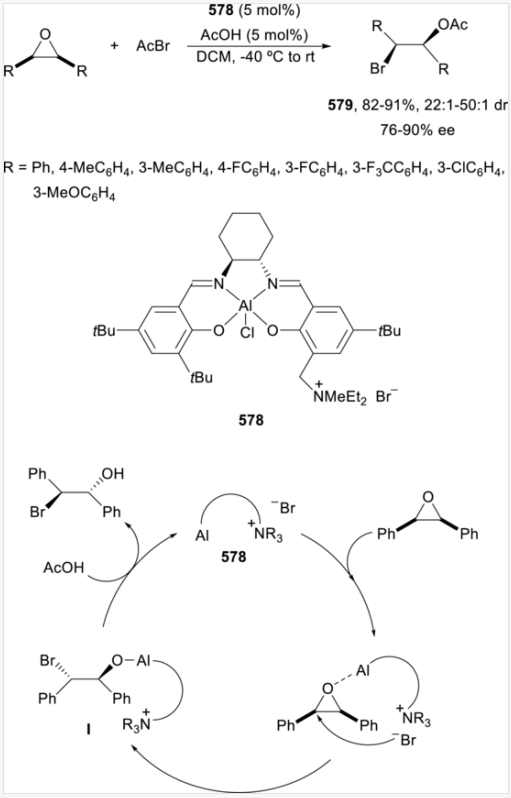


Dy-Catalyzed desymmetrization of *meso*-epoxides **575** by an enantioselective thiolysis/elimination sequence with **576**.

A bifunctional Lewis acid/ammonium salt catalyst **578** has been used for epoxide desymmetrization with acetyl bromide by Peters and co-workers [319]. This Al-salen complex **578** bearing a diethylmethylammonium bromide moiety catalyzed the reaction with AcBr to deliver enantioenriched acetyl protected bromohydrins **579** in good yields, very high diastereoselectivities and good enantioselectivities (Scheme 180). In the proposed mechanism, the epoxide is activated by coordination to Al. Bromide anion is delivered by the internal ammonium moiety providing alkoxide **I**, which is protonated by AcOH present in the reaction medium. The resulting bromohydrin is acetylated by AcBr to provide the final product.

alt-text: Scheme 180

Scheme 180

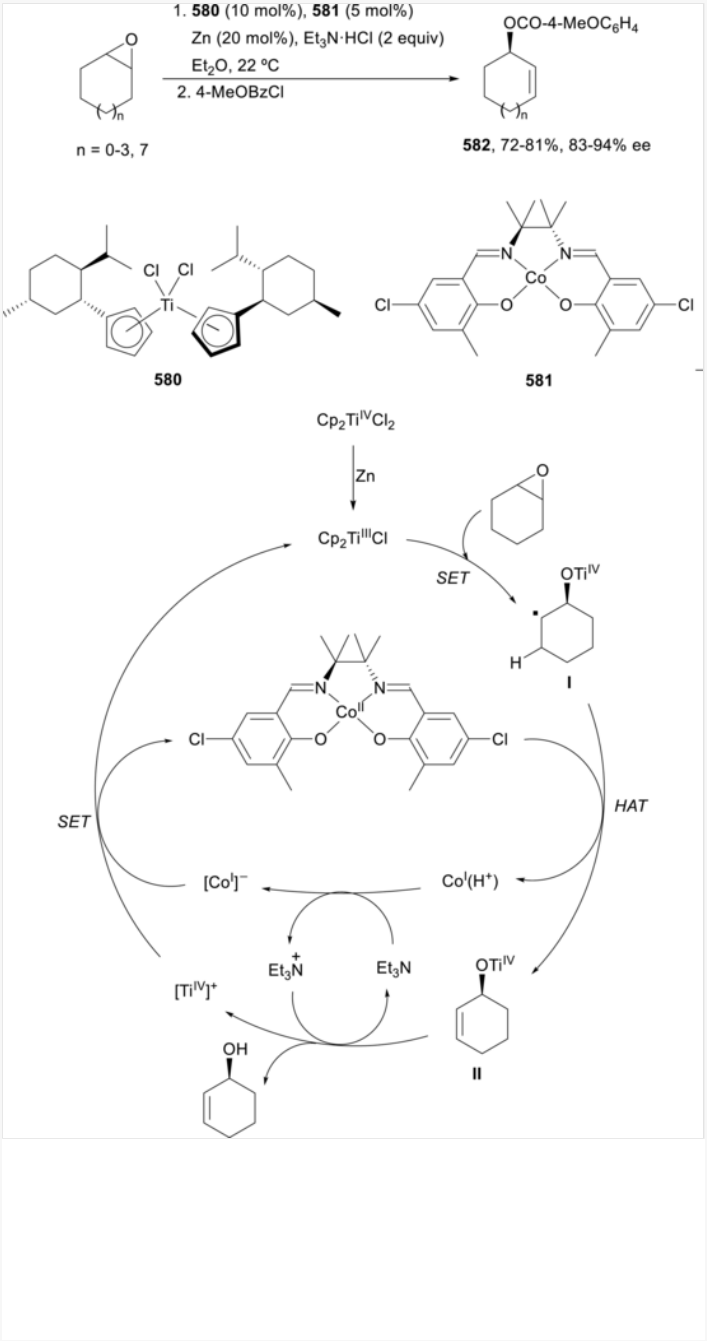


Al-Salen-ammonium salt-catalyzed desymmetrization of epoxides by an enantioselective ring opening with acetyl bromide.

The rearrangement of epoxides to form allylic alcohols has been mainly carried out under strong base-mediated conditions. Lin and co-workers [320] have recently reported this enantioselective isomerization of cyclic *meso*-epoxides to allylic alcohols followed by benzoylation to give products **582** (Scheme 181). In this case, a Ti/Co dual catalytic system formed by Kagan's complex **580** and co-salen **581** are the promoter of the redox-relay catalysis initiated by homolytic epoxide ring opening and followed by hydrogen atom transfer (HAT), respectively. The proposed mechanism involves the formation of $CpTi^{III}Cl$ *via* Zn reduction of $Cp_2Ti^{IV}Cl_2$, triggering one electron reduction of epoxide to radical **I**. This radical **I** is transformed into alkoxide **II** to produce $Co^{I}(H^{+})$ intermediate, which undergoes proton transfer/electron transfer (PT/ET) to regenerate Co^{II} and Ti^{III} mediated by Et_3N.

alt-text: Scheme 181

Scheme 181

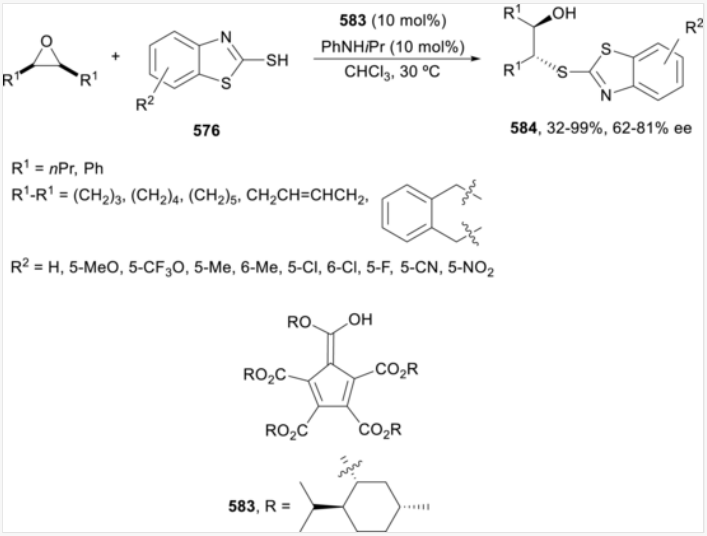


Ti/Co-Catalyzed desymmetrization of cyclic epoxides to allylic alcohols by an enantioselective radical redox-relay.

Organocatalyzed desymmetrization of epoxides [12,321] has been carried out mainly with chiral phosphoric acids (CPA) [322,323]. This particular desymmetrization with CPA has been recently covered by Liu and Yang [323]. Alternatively Lambert's pentacarbonylcyclopentadiene (PCCP) [324] based chiral Brønsted acid **583** in combination of *N*-isopropylaniline as amine additive has been used for the desymmetrization of cyclic and acyclic *meso*-epoxides by 2-mercaptobenzothiazoles (**576**) [325]. The resulting ring opening products **584** were obtained with up to 99% yield and 81% ee (Scheme 182).

alt-text: Scheme 182

Scheme 182

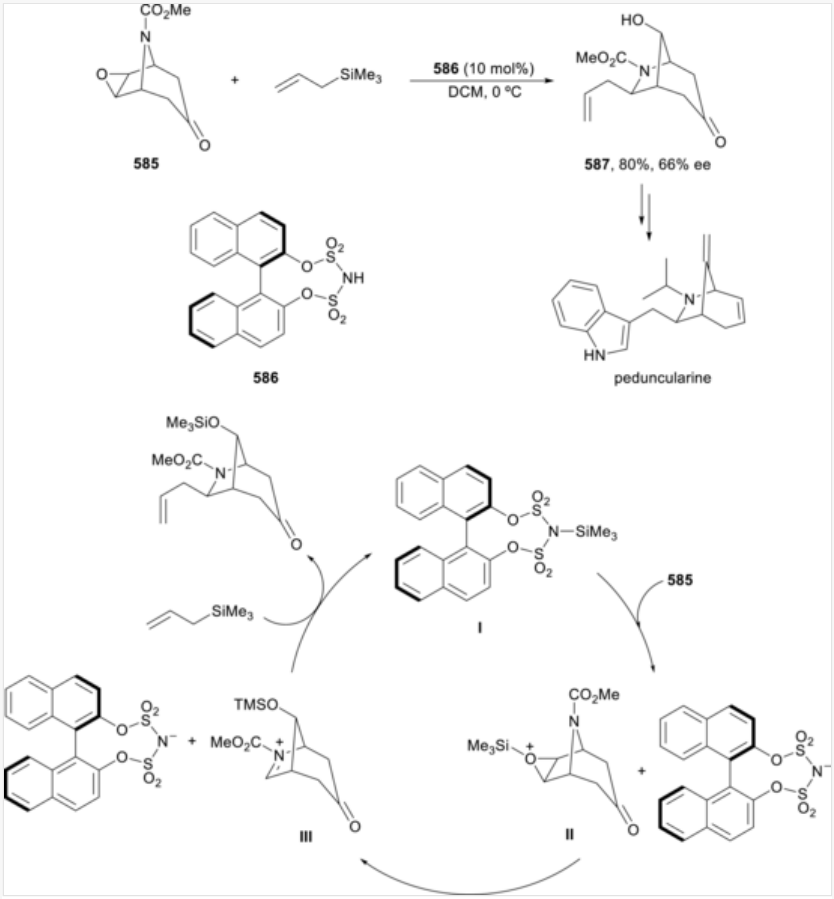


Brønsted acid-catalyzed desymmetrization of epoxides by an enantioselective ring opening with **576**.

Hodgson and co-workers [326] recently reported the enantioselective desymmetrization of an epoxytropinone **585** for peduncularine synthesis. Instead of bases, a BINOL derived bis(sulfuryl)imide **586** as organocatalyst and by reaction with allyltrimethylsilane induced a nitrogen-driven rearrangement iminium-trapping cascade in an enantioselective manner to give product **587** in 80% yield and with 66% ee (Scheme 183). A suggested catalytic cycle for the rearrangement-allylation involves the silylation of **586** to give catalyst **I** able to silylate the epoxide giving intermediate **II**. This oxonium intermediate **II** undergoes ring opening involving σ-bond participation to furnish iminium intermediate **III**. Final iminium trapping by allyltrimethylsilane leads to the formation of *O*-silylated **587**.

alt-text: Scheme 183

Scheme 183



Organocatalyzed desymmetrization of oxirane **585** by an enantioselective rearrangement iminium-trapping cascade.

Enzymatic hydrolytic desymmetrization of epoxides has been carried out by Reetz and co-workers with mutants limonene epoxide hydrolase (LEH) [327–330]. Controlling several parameters in the direct evolution of the enzyme such as thermostability, enantioselectivity and activity. Specially using iterative saturation mutagenesis desymmetrization of cyclohexene oxide gave (*R,R*)- and (*S,S*)-cyclohexane-1,2-diol with different LEH variants with ee in the range 80–94% at temperatures between 5 and 10 °C [329]. The crystal structures of these LEH combined with theoretical computations for cyclopentene and cyclohexene oxide allowed insight into mechanistic details and guidance for future protein engineering of selective LEH mutants.

8.2 Oxetanes

Desymmetrization of 3-monosubstituted and 3,3-disubstituted oxetanes [12,13,323] has been performed mainly by nucleophilic ring opening using Lewis and Brønsted acids (generally CPAs) and has been recently reviewed by Sandvoβ and Wiest [331]. This methodology allows the synthesis of highly functionalized three-carbon chiral building blocks when intermolecular nucleophiles are used and of cyclic saturated heterocycles in intramolecular processes.

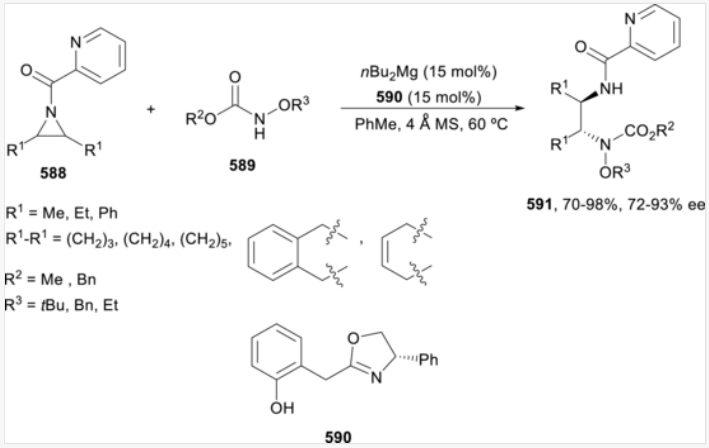
8.3 Aziridines

As in the case of epoxides, nucleophilic ring opening of aziridines is the most common strategy for desymmetrization reactions [13,322,332]. Wang and co-workers have reported Mg(II)-catalyzed enantioselective desymmetrization reactions of *meso*-aziridines with nitrogen-containing nucleophiles [333]. Enantioenriched 1,2-diamine derivatives **591**

were prepared by reaction of cyclic and acyclic aziridines **588** with protected hydroxylamines **589** using nBu$_2$Mg and the box ligand **590** (Scheme 184) [333]. This process only works with these types of hydroxylamines and the substitution by a 2-pyridyl group in the acylated aziridine **588** was also crucial.

alt-text: Scheme 184

Scheme 184

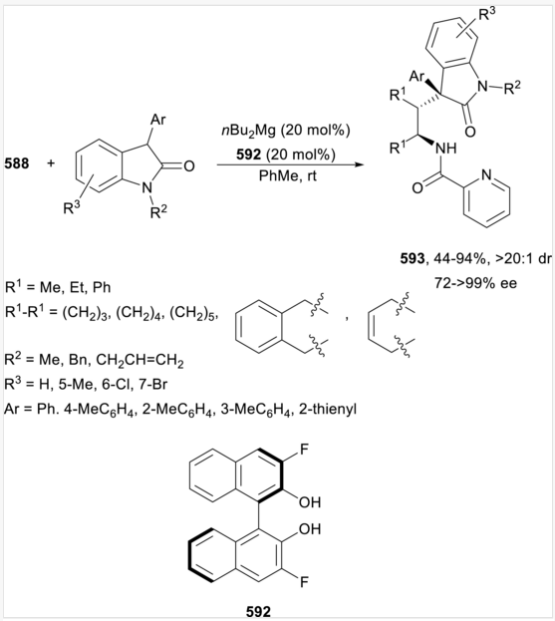


Mg-Catalyzed deymmetrization of *meso*-aziridines **588** by an enantioselective ring opening with hydroxylamine derivatives **589**.

The use of carbon nucleophiles was previously described by the same group [334]. 3-Aryloxindoles were used as nucleophiles for the ring opening of *N*-(2-picolinoyl)aziridines **588** under Mg-catalysis in the presence of 3,3′-fluorinated-BINOL (**592**) (Scheme 185). A series of enantioenriched 3-alkyl-3-aryl oxindoles **593** were obtained in good yields, diastereo- and enantioselectivities.

alt-text: Scheme 185

Scheme 185

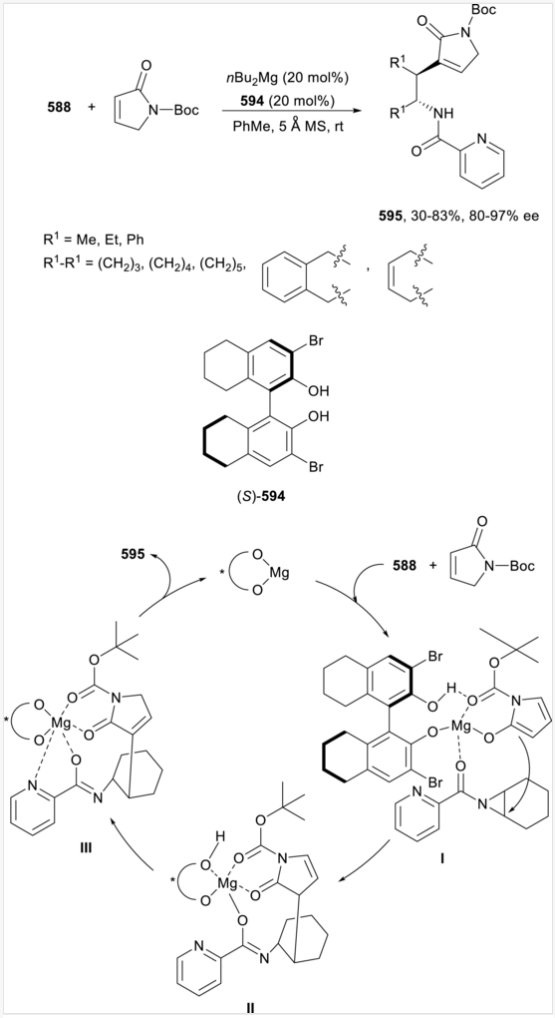


Mg-Catalyzed desymmetrization of *meso*-aziridines **588** by an enantioselective ring opening with oxindoles.

A Mg catalyst generated from nBu$_2$Mg and (*S*)-3,3′-dibromo-8*H*-BINOL (**594**) has been used in desymmetrization of *meso*-aziridines **588** with a α,β-unsaturated γ-butyrolactam (Scheme 186) [335]. In this case, the α-sp^2-carbon of the lactam is bonded to the final products **595**, which were obtained in good yields and enantioselectivities. A catalytic cycle was proposed in which firstly takes place the γ-deprotonation of the *N*-Boc lactam coordinated with the Mg binolate in intermediate **I**. The activated lactam in **I** would attack the *meso*-aziridine provoking the ring opening (intermediate **II**). Next, after a second deprotonation of the α-carbon of the butyrolactam and an isomerization process (intermediate **III**) could release the product and regenerated the Mg catalyst. This process was also carried out with (*R*)-**594** giving *ent*-**595** with similar results.

alt-text: Scheme 186

Scheme 186

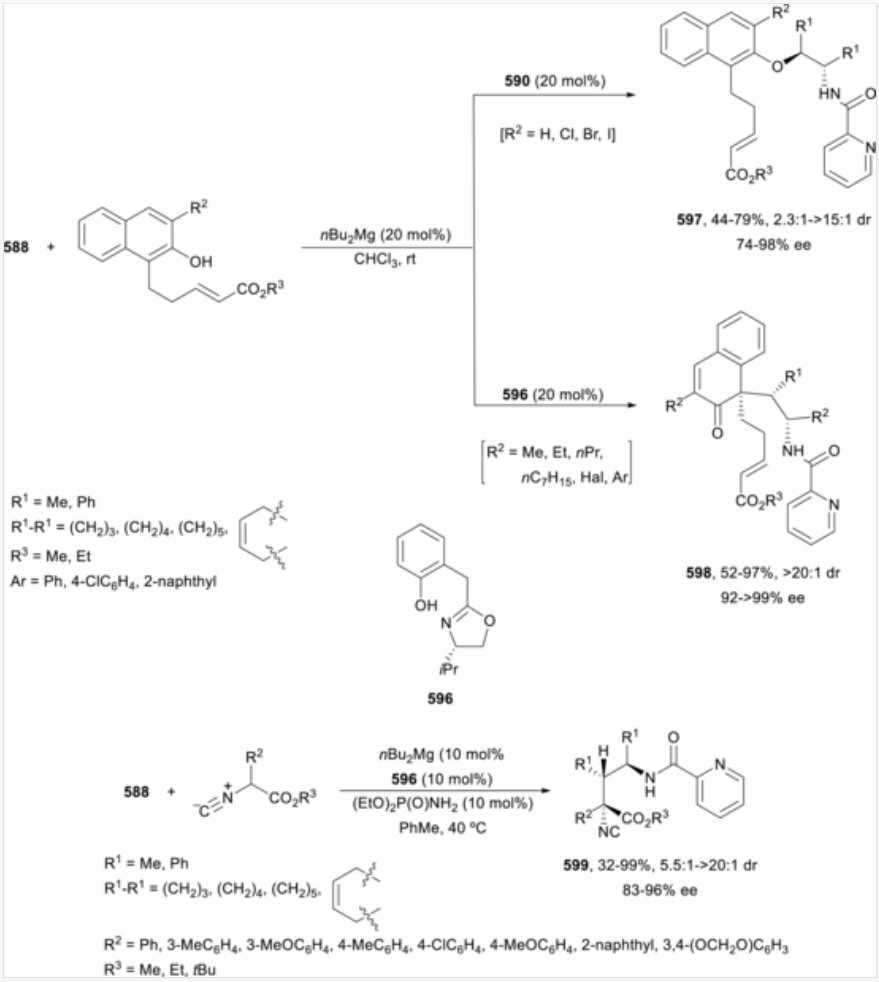


Mg-Catalyzed desymmetrization of *meso*-aziridines **588** by an enantioselective ring opening with *N*-Boc-α,β-unsaturated γ-butyrolactam.

The group of Wang has described two more desymmetrizations of aziridines **588** with naphthols [335] and α-isocyanoacetates [337] under Mg catalysis and oxazolines as chiral ligands (Scheme 187). In the case of naphthols, regiodivergent [33] processes were observed depending of substituents at the 3-position of the substrate and the ligand. Using oxazoline **590**, *O*-alkylated products **597** were obtained when the naphthol has at C3 a hydrogen or a halogen. On the other hand, ligand **596** provided products **598** resulting from a dearomatization process, when naphthols have mainly an alkyl or aryl group at the 3-position [336]. The reaction of α-isocyanoacetates with *meso*-aziridines **588** was performed using nBu$_2$Mg and ligand **596** and in the presence of diphenylphosphinamide to furnish products **599** in good yields, diastereo- and enantioselectivities [337]. These products can be further transformed into tetrahydropyrimidines with a silver catalyst.

alt-text: Scheme 187

Scheme 187

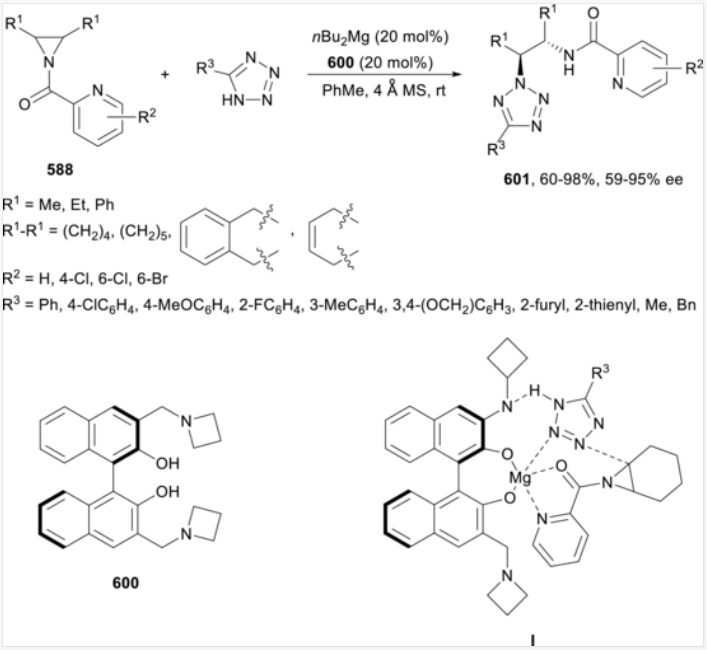


Mg-Catalyzed desymmetrization of *meso*-aziridines **588** by an enantioselective ring opening with naphthols or α-isocyanoacetates.

Substituted tetrazoles have been used as nucleophiles in the desymmetrization of *meso*-aziridines **588** under Mg catalysis by Yang, Wang and co-workers [338]. In the same case, a BINOLAM [339] derived ligand **600** gave products **601** in high yields and with good enantioselectivities (Scheme 188). The bifunctional character of this ligand is represented on the intermediate **I** depicted in Scheme 188.

alt-text: Scheme 188

Scheme 188

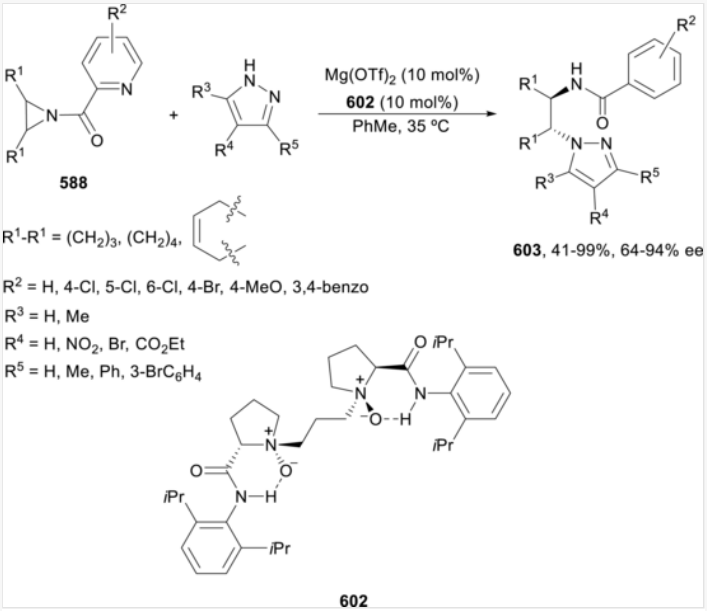


Mg-Catalyzed desymmetrization of *meso*-aziridines **588** by an enantioselective ring opening with tetrazoles.

Feng and co-workers [340] reported the ring opening of cyclic *meso*-aziridines **588** with pyrazoles using *N,N′*-dioxide-Mg(OTf)$_2$ complex as the catalyst, prepared *in situ* from ligand **602** (Scheme 189). The corresponding products **603** were obtained in good to excellent yields and good enantioselectivities. Besides, benzotriazole, phenyltetrazole and trimethylsilyl azide were also applied in this desymmetrization process with moderate results.

alt-text: Scheme 189

Scheme 189

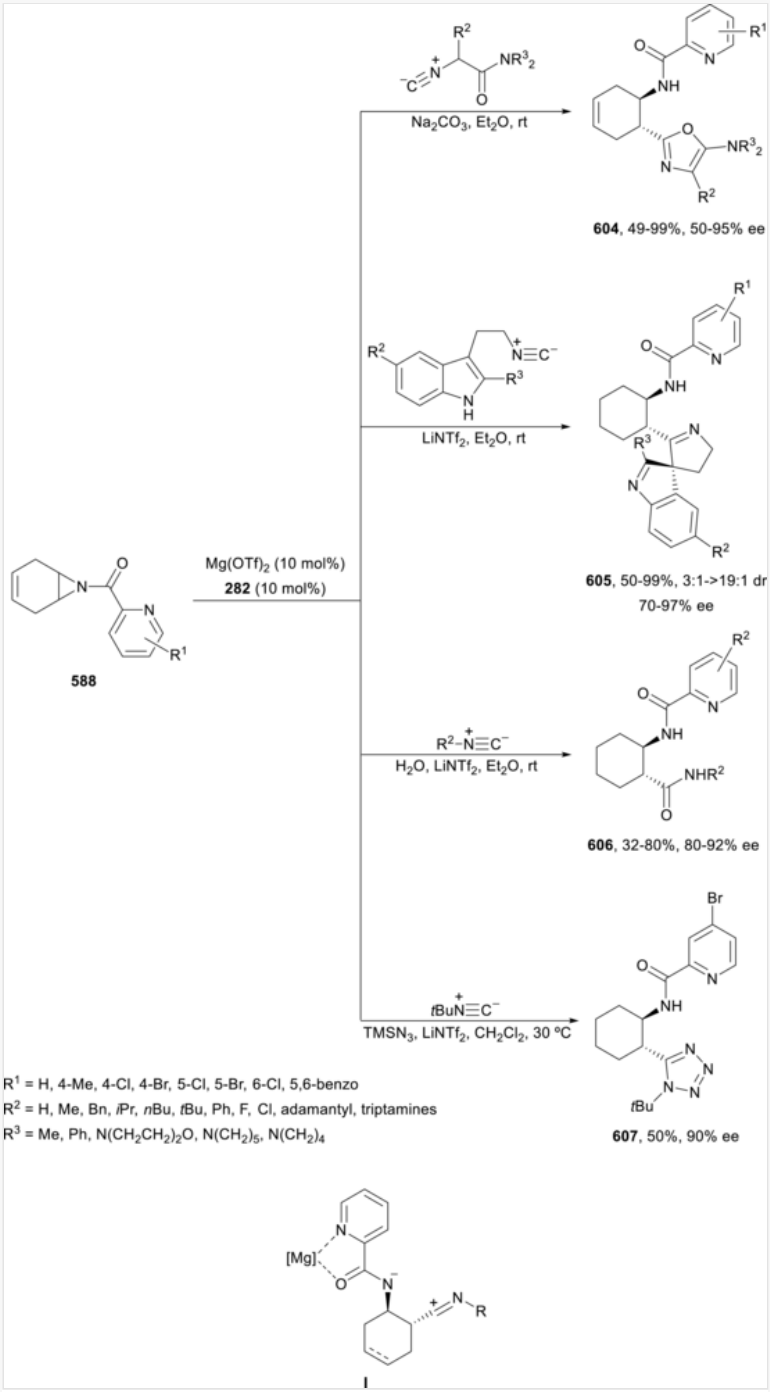


Mg-Catalyzed desymmetrization of *meso*-aziridines **588** by an enantioselective ring opening with pyrazoles.

The same group [341] used a related ligand **282** for the desymmetrization of cyclohexane derived *meso*-aziridines **588** [R^1-R^1 = $(CH_2)_4$] by reaction with isocyanides as nucleophiles to give zwitterionic intermediates **I**, which were trapped by intramolecular oxygen- or carbon-based nucleophiles to provide amino-oxazoles **604** or spiroindolines **605**, respectively (Scheme 190). In the presence of water the 1,4-zwiterionic intermediate delivered β-amino amides **606** and in the presence of $TMSN_3$ tetrazole derivative **607** was formed.

alt-text: Scheme 190

Scheme 190

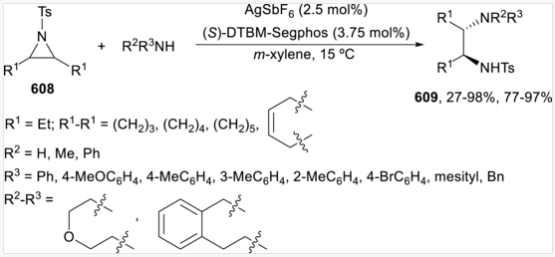


Mg-Catalyzed desymmetrization of *meso*-aziridines **588** by an enantioselective ring opening with isocyanides.

Under silver catalysis, Chai and co-workers [342] described the enantioselective aminolysis of *N*-tosylaziridines **608** with anilines and aliphatic amines. Using (*S*)-DTBM-Segphos as a chiral ligand and $AgSbF_6$, the corresponding diamine derivatives **609** were obtained in moderate to high yields and good enantioselectivities (Scheme 191).

alt-text: Scheme 191

Scheme 191

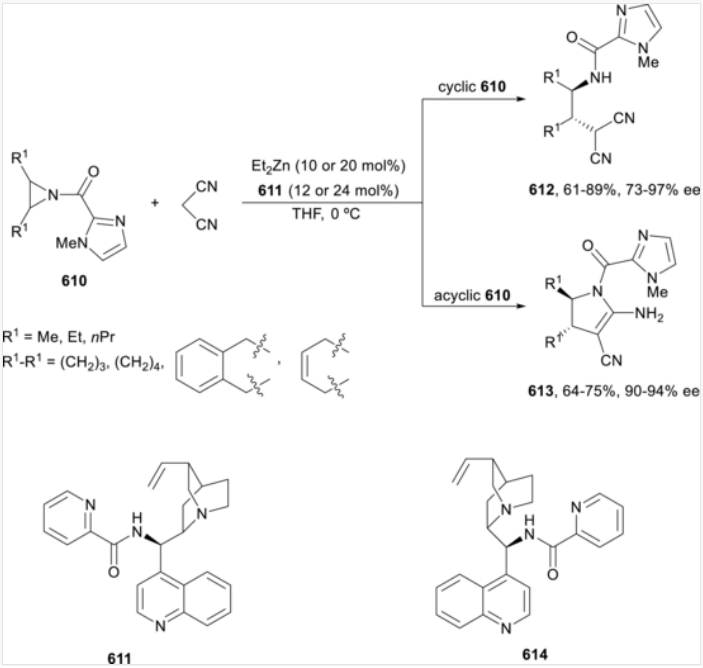


Ag-Catalyzed desymmetrization of *N*-tosyl aziridines **608** by an enantioselective aminolysis.

Cinchona alkaloid derivative **611** and Et_2Zn have been used as catalysts by Nakamura and co-workers [343] for the ring opening of *N*-acyl aziridines **610** with malononitrile (Scheme 192). In the case of cyclic aziridines resulted products **612** by intermediacy of complex **I**, in which the zinc cation is coordinated in a tetrahedral form by the carbonyl oxygen and the nitrogen of the imidazolyl group, and the quinuclidine moiety forms a hydrogen bond with malononitrile. Acyclic aziridines gave 2,3-dihydro-1*H*-pyrrole compounds **613** by intramolecular nucleophilic addition of the amide nitrogen to the cyano group. Cinchonine derivative **614** gave product **612** [R^1-R^1 = $(CH_2)_4$] having opposite configuration in 75% yield with 94% ee.

alt-text: Scheme 192

Scheme 192

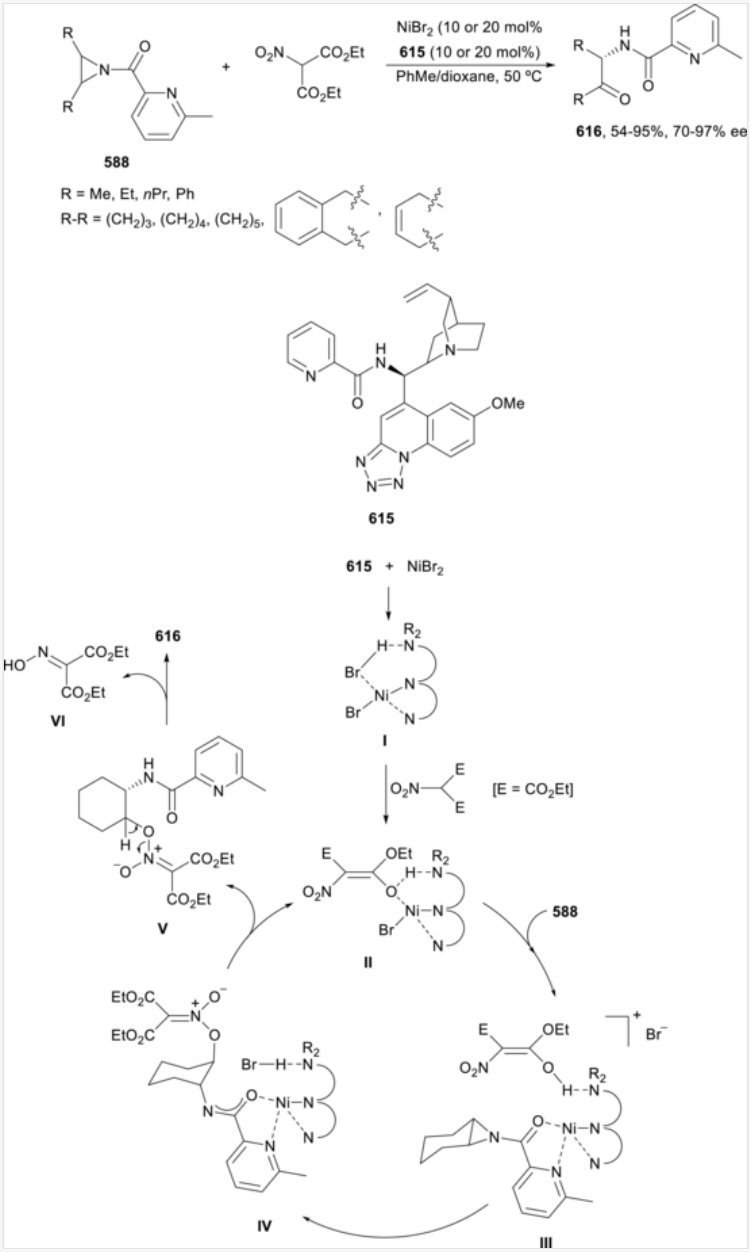


Zn-Catalyzed desymmetrization of *meso*-aziridines **610** by an enantioselective ring opening with malononitrile.

The same group [344] previously described an oxidative ring opening of aziridines **588** with ethyl α-nitromalonate using *Cinchona* alkaloid derivative **615** and $NiBr_2$ as catalysts to provide products **616** (Scheme 193). In the proposed catalytic cycle, firstly takes place the formation of complex **I** by coordination of the ligand with $NiBr_2$, which reacts with diethyl α-nitromalonate to form intermediate **II**. Then, the attack of aziridines occurs giving intermediate **III**, which undergoes ring opening to provide intermediate **IV**. This last intermediate **IV** suffers deprotonation and decomplexation to afford intermediate **V**. Final oxy-Cope-type elimination of intermediate **V** leads to product **616** and the oxime derivative **VI**.

alt-text: Scheme 193

Scheme 193

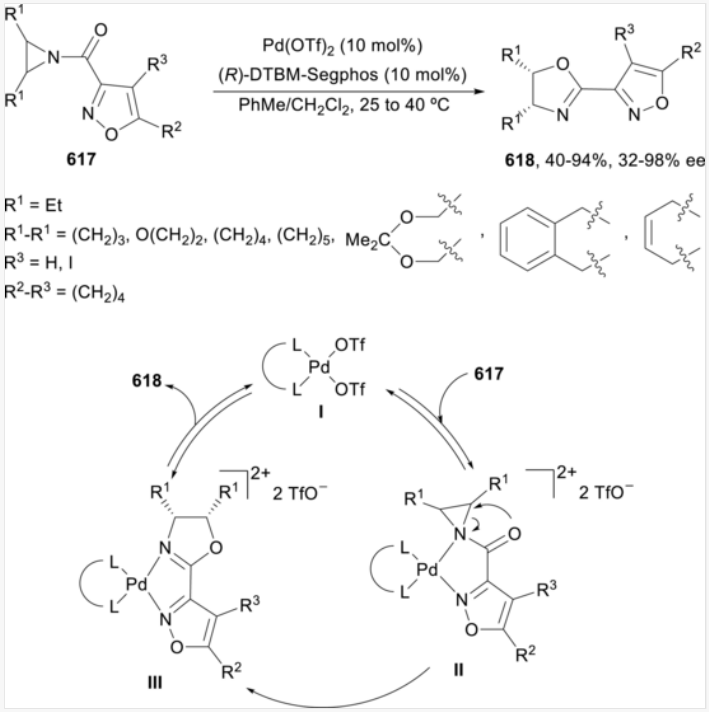


Ni-Catalyzed desymmetrization of *meso*-aziridines **588** by an enantioselective oxidative ring opening with ethyl nitromalonate.

An enantioselective Heine reaction has been used for desymmetrization of *N*-acylaziridines **617** under Pd catalysis by Morgan and co-workers [345]. These aziridines **617** underwent rearrangement by ring expansion in the presence of $Pd(OTf)_2$ and (*R*)-DTBM-Segphos to provide highly enantioenriched oxazoline products **618** (Scheme 194). In the proposed mechanism the catalyst **I** coordinates the aziridine to form intermediate **II**, which by a S_Ni mechanism gives intermediate **III**. Finally intermediate **III** releases the product and regenerates the catalyst.

alt-text: Scheme 194

Scheme 194

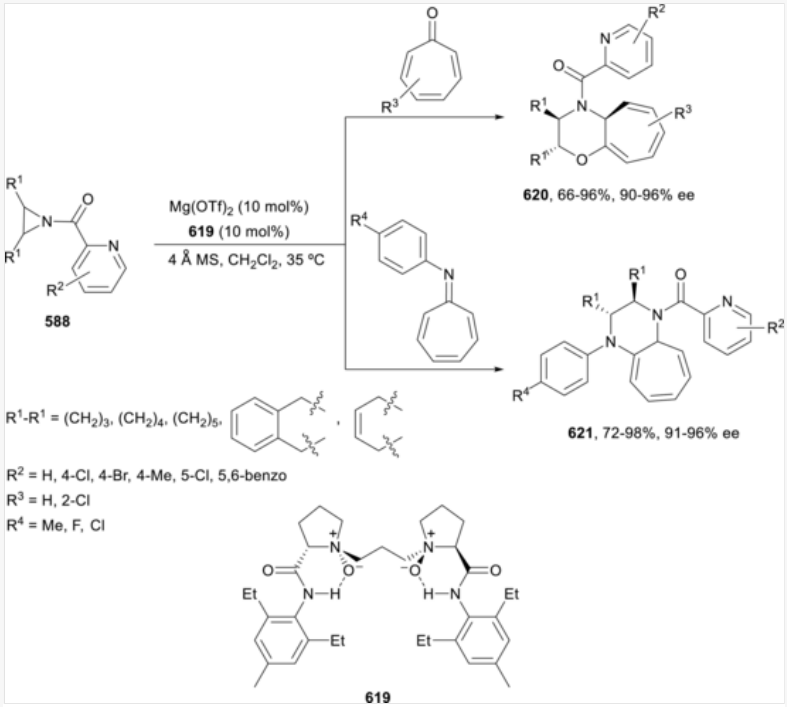


Pd-Catalyzed desymmetrization of *meso*-aziridines **617** by an enantioselective Heine reaction.

Under $Mg(OTf)_2$/*N,N′*-dioxide **619** catalysis an enantioselective [8 + 3] annulation of cyclic aziridines **588** with tropones or azaheptafulvenes took place to afford tetrahydrocyclohepta[*b*] [1,4]oxazines **620** or tetrahydro-1*H*-cycloheptapyrazines **621** in good yields and with excellent diastereo- and enantioselectivities (Scheme 195) [346].

alt-text: Scheme 195

Scheme 195

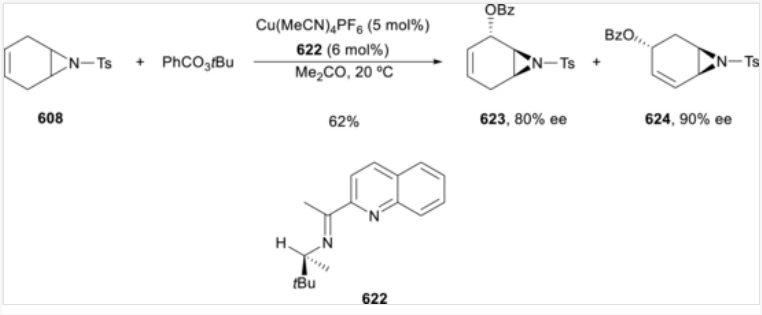


Mg-Catalyzed desymmetrization of *meso*-aziridines **588** by enantioselective [8 + 3] annulation with tropones and azaheptafulvenos.

Hayashi and co-workers [347] recently reported a regiodivergent [33] desymmetrization of *N*-tosyl *meso*-azabicycloheptene **608** *via* allylic oxidation under Cu catalysis. Two regioisomers **623** and **624** (1:1) were isolated in 62% yield using *tert*-butyl perbenzoate as oxidant and chiral ligand **622** (Scheme 196). In one of the proposed reaction pathways two Cu(III)-π-allyl intermediates **I** and **II** are formed in a 1:1 ratio, which will form the σ-allyl-Cu(III) complexes **III** and **IV**, respectively. Attack by the benzoate carbonyl oxygen to the opposite side of the aziridine moiety would afford products **623** and **624**.

alt-text: Scheme 196

Scheme 196



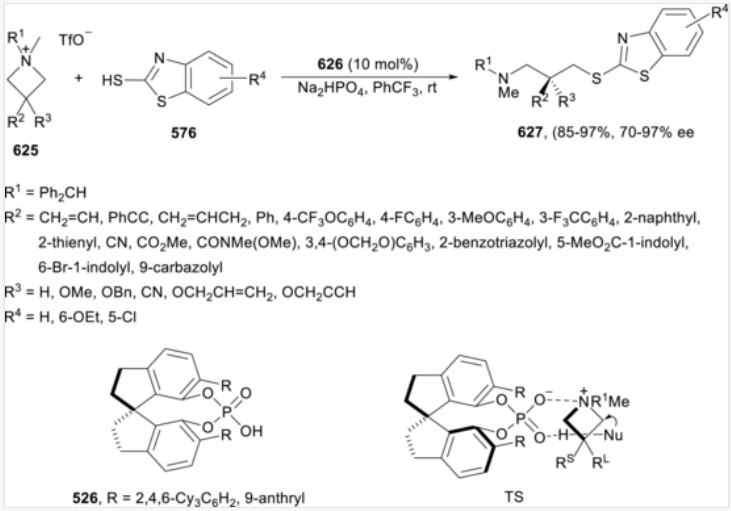
Cu-Catalyzed desymmetrization of *meso*-aziridine **608** by an enantioselective allylic oxidation.

8.4 Azetidines

Azetidines showed a relative stability towards nucleophilic ring opening. Using CPAs catalysis [12,13,332] the corresponding amines are obtained. However, azetidinium salts **625** [348] underwent easier ring opening using 2-mercaptobenzothiazoles (**576**) as nucleophiles than the precursor azetidines [349]. Starting azetidinium salts **625** were prepared by reaction of *N*-substituted azetidines with methyl triflate. Spinol-derived chiral phosphoric acids **626** gave products **627** in high yields and enantioselectivities under mild reaction conditions (Scheme 197). The counterion of the azetidinium induced asymmetric control in the ring opening forming an ion-pair which according to TS the nucleophile approaches the back side.

alt-text: Scheme 197

Scheme 197



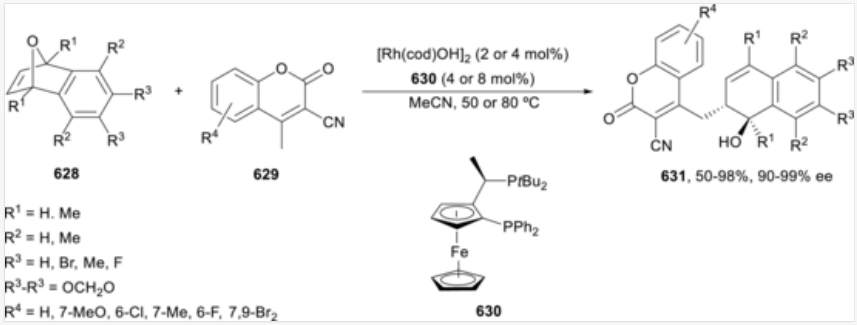
Phosphoric acid-catalyzed desymmetrization of azetidinium salts **625** by an enantioselective ring opening with **576**.

8.5 Oxa- and aza-benzonorbornadienes

The asymmetric ring opening (ARO) of oxa/azabenzonorbornadienes by nucleophiles to generate substituted chiral dihydronaphthalenes has been pioneered by Lautens [350]. Recent developments in this area by Lauten's group described the Rh-catalyzed ARO of oxabicycles **628** with coumarins **629** using (*R,S*)-PPF-P*t*Bu$_2$ (**630**) as a chiral ligand [351]. The vinylogous reactivity of cyanocoumarins **629** as a γ-nucleophile provided products **631** in good to high yields and enantioselectivities (Scheme 198). This methodology has been applied to the synthesis of a range of compounds structurally similar to anticoagulants and rodenticides such as difenacoum.

alt-text: Scheme 198

Scheme 198

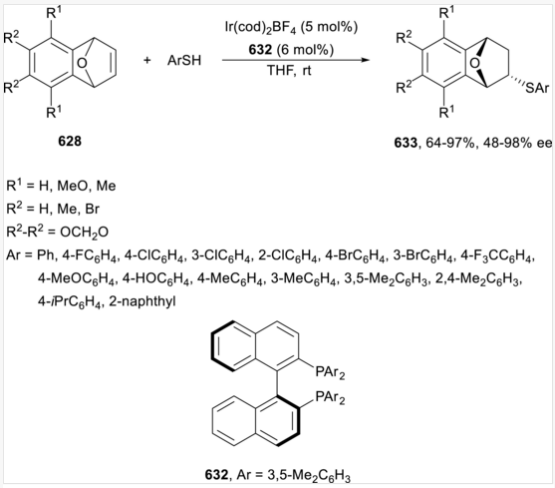


Rh-Catalyzed desymmetrization of *meso*-oxabenzonorbornadienes **628** by an enantioselective ring opening with coumarins **629**.

Alternatively to ARO reactions, asymmetric ring addition of nucleophiles to the C=C can take place depending on the catalyst. Wang and co-workers [352] described the Ir-catalyzed addition of thiophenols to oxabenzonorbornadienes **628**. Exclusively thiol addition *exo*-products **633** were formed in high yields and enantioselectivities using (*S*)-Xyl-BINAP (**632**) as a chiral ligand (Scheme 199).

alt-text: Scheme 199

Scheme 199



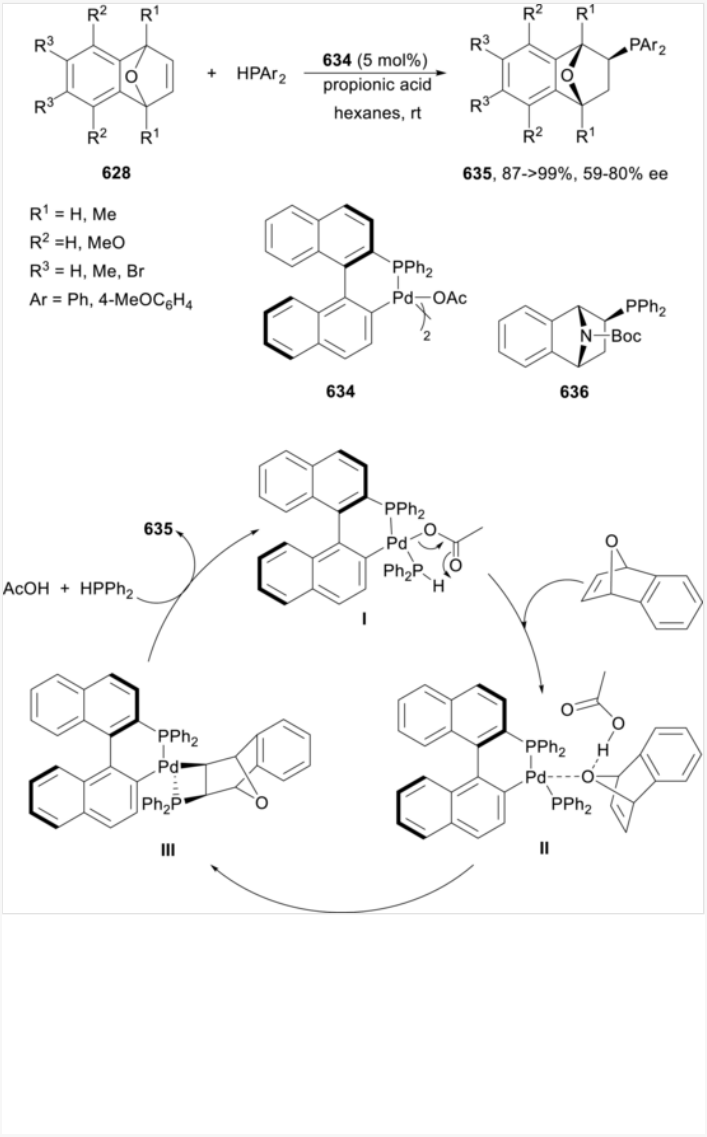
Ir-Catalyzed desymmetrization of *meso*-oxabenzonorbornadienes **628** by an enantioselective addition of thiophenols.

Catalytic asymmetric hydrophosphination of oxabenzonorbornadienes **628** takes place using a chiral phosphapalladacycle **634** to afford addition products **635** in high yields and moderate enantioselectivities (Scheme 200) [353]. The presence of an aliphatic carboxylic acid such as propionic acid in hexane as solvent were crucial to improve the results. Therefore a plausible mechanism was proposed in which the palladacycle coordinates $HPPh_2$ *trans* to the phosphine to provide complex **I**. Next, intermediate **II** could be formed by coordination of Pd with the oxabicycle **628** protonated by acetic acid. Phosphination of the double bond forms intermediate **III**, which by

protonolysis gives rise to the product. This process has been carried out with *N*-Boc-azabenzonorbornadiene to give the addition product **636** in >99% yield and 88% ee.

alt-text: Scheme 200

Scheme 200



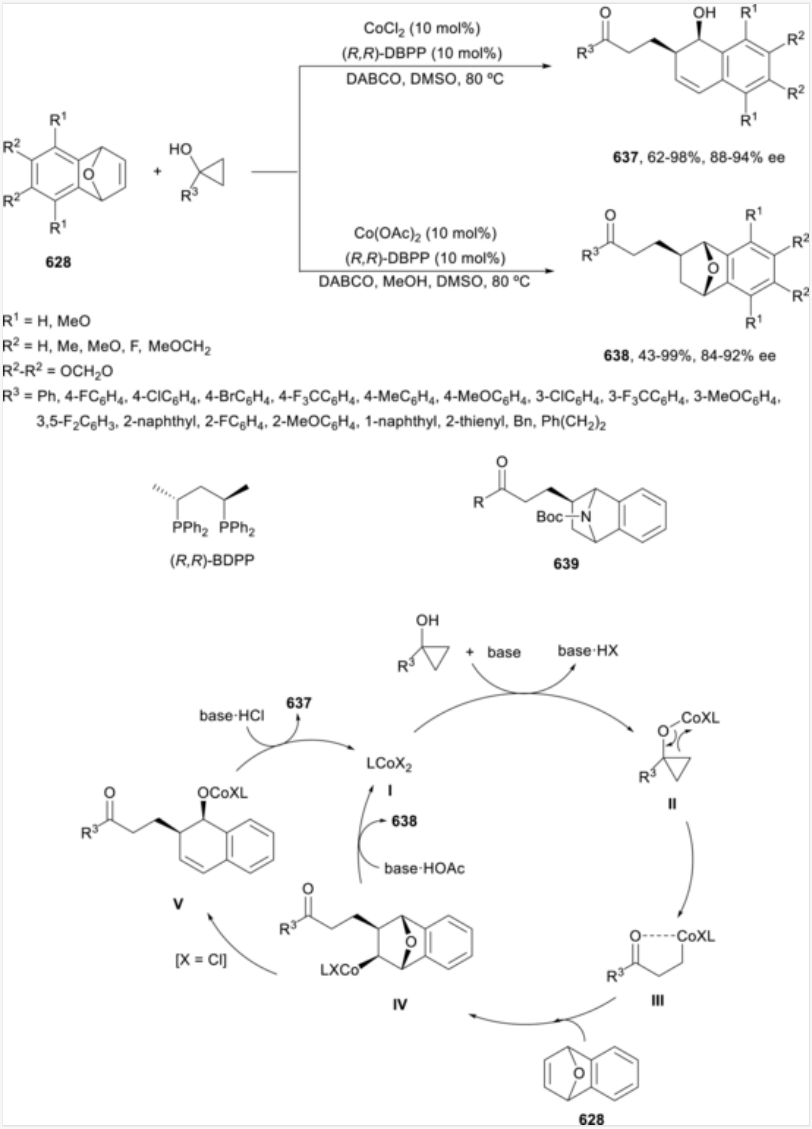
Pd-Catalyzed desymmetrization of *meso*-oxabenzonorbornadienes **628** by an enantioselective hydrophosphination.

Enantioselective and chemodivergent [354] addition of cyclopropanols to oxabicyclic alkenes **628** took place under Co catalysis [355]. In the presence of $CoCl_2$ and (*R,R*)-BDPP, ARO reaction occurred to provide 1,2-dihydronaphthalene-1-ol derivatives **637** in good yields with high enantioselectivities (Scheme 201). By contrast, $Co(OAc)_2$ and the same chiral ligand in the presence of MeOH afforded hydroalkylation products **638** with similar level of enantioselectivity. In the proposed mechanism, a diphosphine-Co species **I** reacts with the cyclopropanol assisted by DABCO to give a Co(II) homoenolate **III**. Carbocobaltation to the oxabicyclic alkene gives rise to an alkylcobalt species **IV**. β-Oxygen elimination of **IV** leads to intermediate **V** and then to the ring opening product **637**. Alternatively, protonolysis of **IV** furnishes the hydroalkylation product **638**. The counterion-dependent chemodivergence between $CoCl_2$ and $Co(OAc)_2$ was explained by formation in the last case of acetic acid which facilitates the protonolysis of intermediate **IV**. The first reaction fails in the case of *N*-Boc-azabenzonorbornadiene, whereas the hydroalkylation gave product **639** in 92% yield and 88% ee.

Images are optimised for fast web viewing. Click on the image to view the original version.

alt-text: Scheme 201

Scheme 201



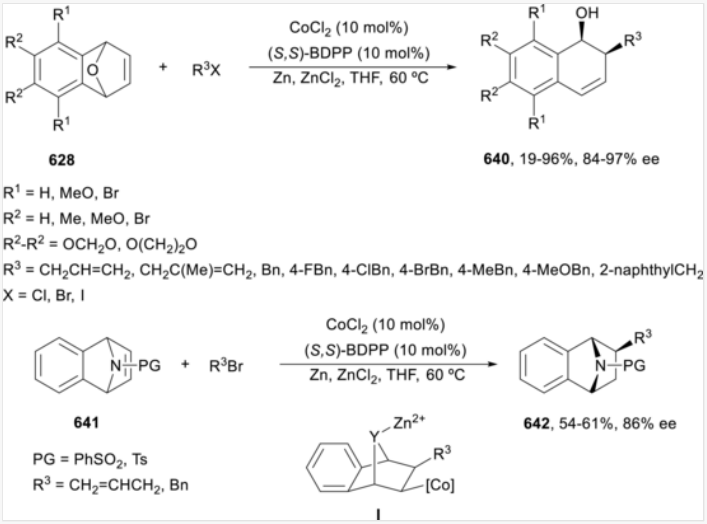
Co-Catalyzed desymmetrization of *meso*-oxabenzonorbornadienes **628** by chemodivergent ring opening or hydroxyalkylation with cyclopropanols.

A Co-catalyzed ARO of oxabenzonorbornadienes **628** with *in situ* generated alkylzinc halides has been described by Fan and co-workers [356]. The catalytic system comprising $CoCl_2$, (*S,S*)-BDPP and $ZnCl_2$ as Lewis acid delivered 1,2-dihydronaphthalen-1-ol derivatives **640** in good yields with high enantioselectivities (Scheme 202). When this methodology was applied to azabenzonorbornadienes **641** the addition products **642** were formed. This divergent behavior was explained by intermediancy of intermediate **I** which by cation exchange gives product **642**, whereas when oxabenzonorbornadiene was used intermediate (Y = O) **I** undergoes β-elimination and rearrangement to afford product **640**.

Images are optimised for fast web viewing. Click on the image to view the original version.

alt-text: Scheme 202

Scheme 202

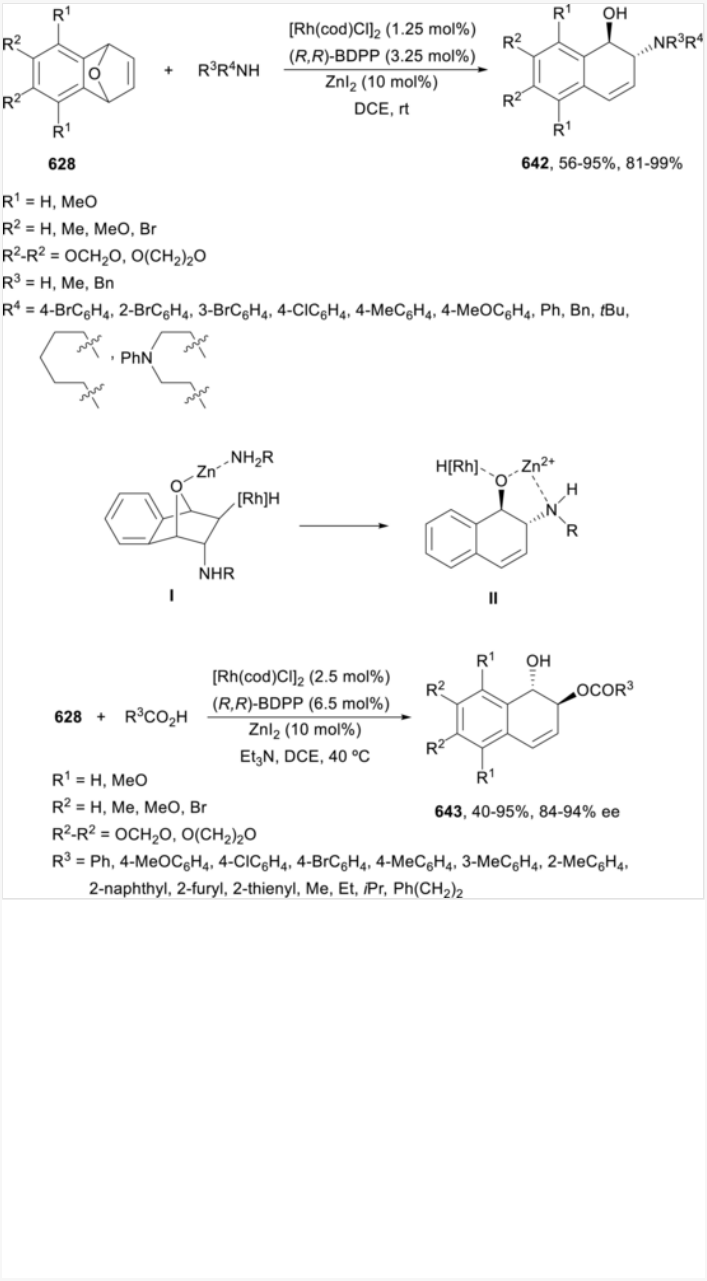


Co-Catalyzed desymmetrization of *meso*-oxa- and azabenzonorbornadienes **628** and **641** by an enantioselective alkylation with *in situ* generated organozinc halides.

The same group has described the Rh-catalyzed ARO reaction of oxabenzonorbornadienes **628** by amines using ZnI_2 as activator and (*R,R*)-BDPP as a chiral ligand. Aromatic and aliphatic amines were suitable heteronucleophiles giving the corresponding β-amino alcohols **642** in good yields with high enantioselectivity (Scheme 203). Intermediate **I** has been proposed as precursor of the ring opened species **II** precursor of the product **642**. In the case of carboxylic acid, they found [358] that this Rh/Zn co-catalyzed ARO reaction worked properly to give the corresponding hydroxynaphthalene derivatives **643** in good yields and with high enantioselectivities (Scheme 203).

alt-text: Scheme 203

Scheme 203

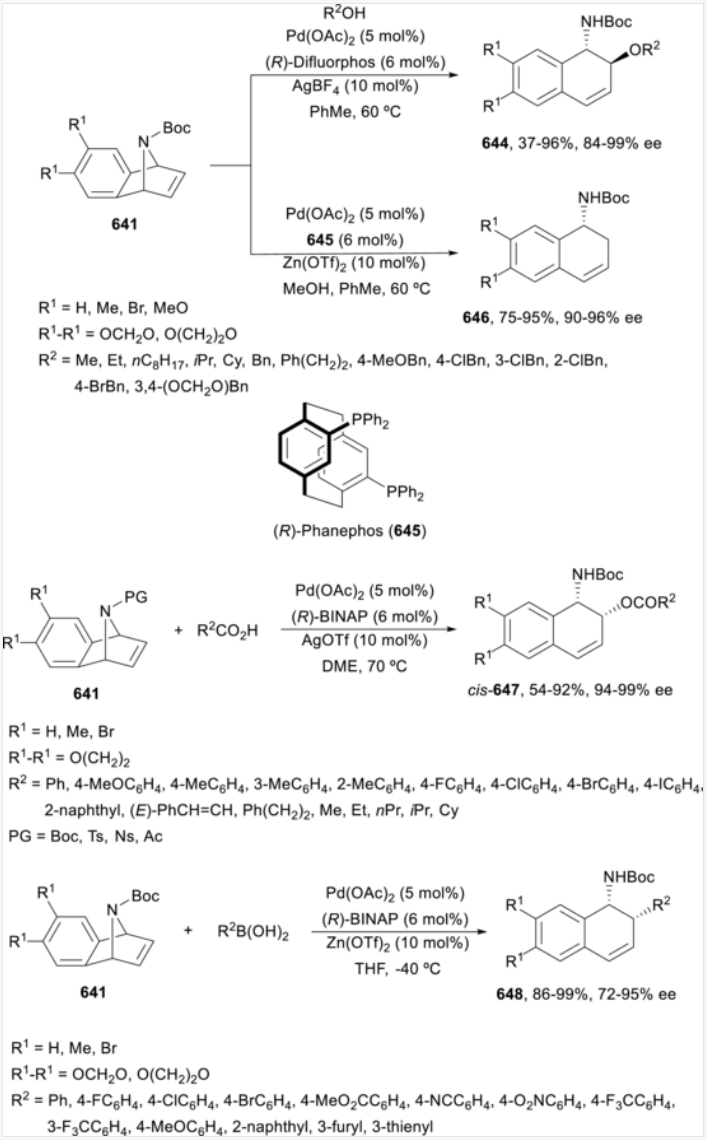


Rh-Catalyzed desymmetrization of *meso*-oxabenzonorbornadieenes **628** by an enantioselective ring opening with amines.

Azabenzonorbornadienes **641** have been submitted to ARO reactions under Pd/Lewis acid co-catalysis with alcohols [359], carboxylic acids [360] and boronic acids [361] by Fan's group. In the case of alcohols, $Pd(OAc)_2$, (*R*)-Difluorphos (*ent*-**540**) and $AgBF_4$ were used as catalytic system to give products **644** [359] (Scheme 204). However, using (*R*)-Phanephos (**645**) as a chiral ligand and $Zn(OTf)_2$ as Lewis acid a reductive ARO reaction took place to provide products **646** by a transfer hydrogenation process with MeOH as reductant. When carboxylic acids were employed as nucleophiles, (*R*)-BINAP as the ligand and AgOTf as Lewis acid gave products *cis*-**647** in good yields and with high enantioselectivities [360] (Scheme 204). In the proposed catalytic cycle, after formation of intermediate **I**, insertion of Pd into the O–H bond of the carboxylic acid gives intermediate **II**. Then, the β-elimination of nitrogen opens the pyrrolidines ring and affords the ring opened species **III**, which evolves regenerating the catalyst and the *cis*-product. In the case of boronic acids, (*R*)-BINAP and $Zn(OTf)_2$ provided chiral 2-substituted naphthalene derivatives **648** up to 99% ee [361] (Scheme 204). The last ARO reaction was carried out with oxabenzonorbornadienes to provide the corresponding 1,2-dihydronaphthalen-1-ol derivatives in 95–96% yields and with 92–98% ee.

alt-text: Scheme 204

Scheme 204

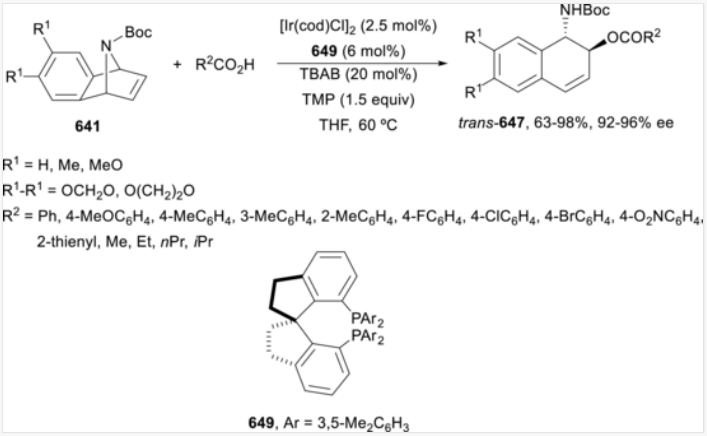


Pd-Catalyzed desymmetrization of *meso*-azabenzonorbornadienes **641** by an enantioselective ring opening with alcohols, carboxylic acids and boronic acids.

Under Ir-catalyzed reaction conditions and spiro ligand (*R*)-Xyl-SDP (**649**), *anti*-stereoselectivity was observed by Fan's group [362] in the ARO reaction of azabenzonorbornadienes **641** with carboxylic acids. In the presence of nBu$_4$NBr (TBAB) as additive and 2,2,6,6-tetramethylpiperidine (TMP) as base, products *trans*-**647** were obtained in good yields with high enantioselectivities (Scheme 205).

alt-text: Scheme 205

Scheme 205



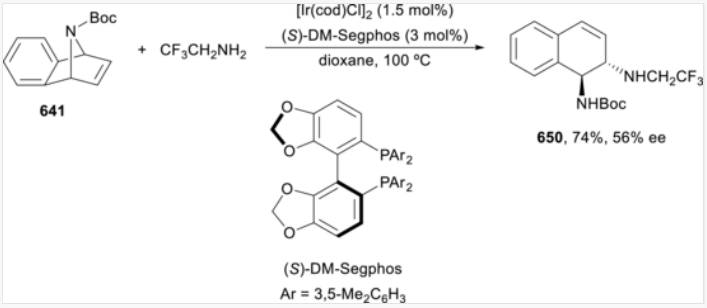
Ir-Catalyzed desymmetrization of *meso*-azabenzonorbornadienes **641** by an enantioselective ring opening with carboxylic acids.

Asymmetric ring opening of azabenzonorbornadienes **641** with aliphatic and aromatic amines was carried out in 2006 by Lautens and co-workers [363] under Rh catalysis and (*S,S'*)-(*R,R'*)-ferriphos as a chiral ligand to give the corresponding *trans*-1,2-diamine derivatives with up to >99% ee. More recently, Yang and co-workers [364] reported the Ir-catalyzed ring opening of azabicycles **641** with fluoralkylamines to provide *trans*-1,2-diamine derivatives **650** in good to excellent yields. The asymmetric ring opening with 2,2,2-trifluoroethylamine to give the enantioenriched diamine **650** only took place in 56% ee using (*S*)-DM-Segphos (Scheme 206).

Images are optimised for fast web viewing. Click on the image to view the original version.

alt-text: Scheme 206

Scheme 206



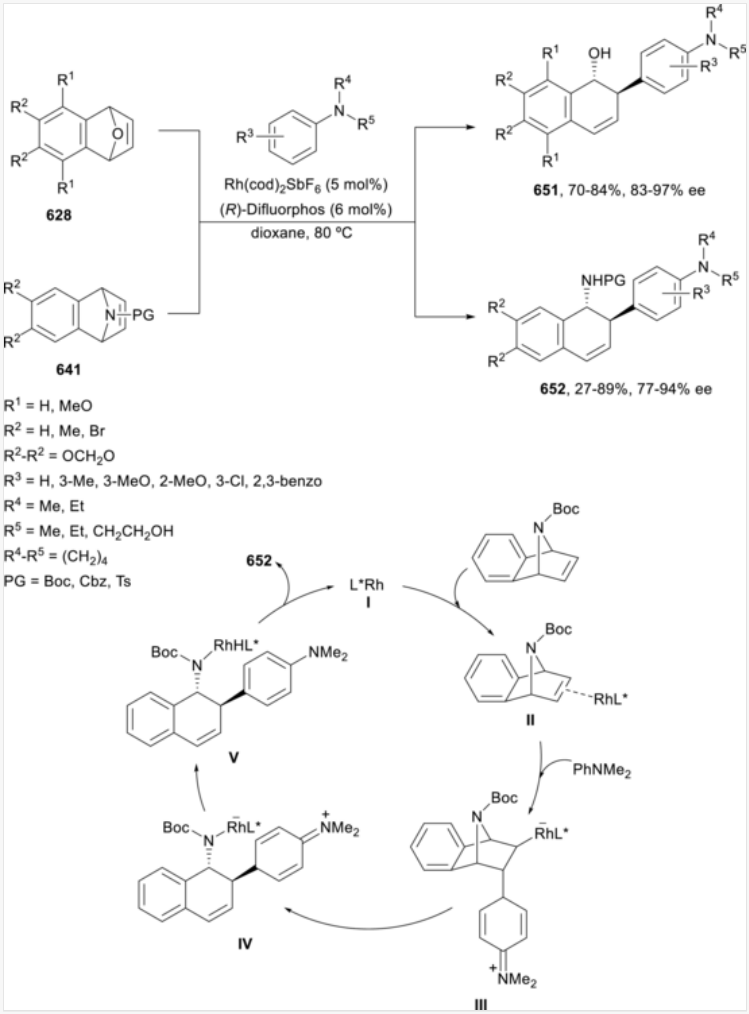
Ir-Catalyzed desymmetrization of *meso*-azabenzonorbornadiene **641** by an enantioselective ring opening with 2,2,2-trifluoroethylamine.

Asymmetric arylative ring opening of oxa and azabenzonorbornadienes **628** and **641** with *N,N*-disubstituted anilines under Rh catalysis has been described by Fan and co-workers [365]. *Via* the Friedel-Crafts (FC) reaction, *trans*-products **651** and **652** were obtained in excellent stereoselectivity (Scheme 207). In the proposed catalytic cycle, the chiral Rh catalyst **I** with Difluorphos (*ent*-**540**) as ligand coordinates the azabenzonorbornadiene **641** to afford intermediate **II**. FC reaction of intermediate **II** with *N,N*-dimethylaniline provides **III**. The β-elimination of nitrogen in intermediate **III** yields species **IV**, which undergoes a proton shift to furnish **V**. Final protonolysis of **V** generates the product.

Images are optimised for fast web viewing. Click on the image to view the original version.

alt-text: Scheme 207

Scheme 207

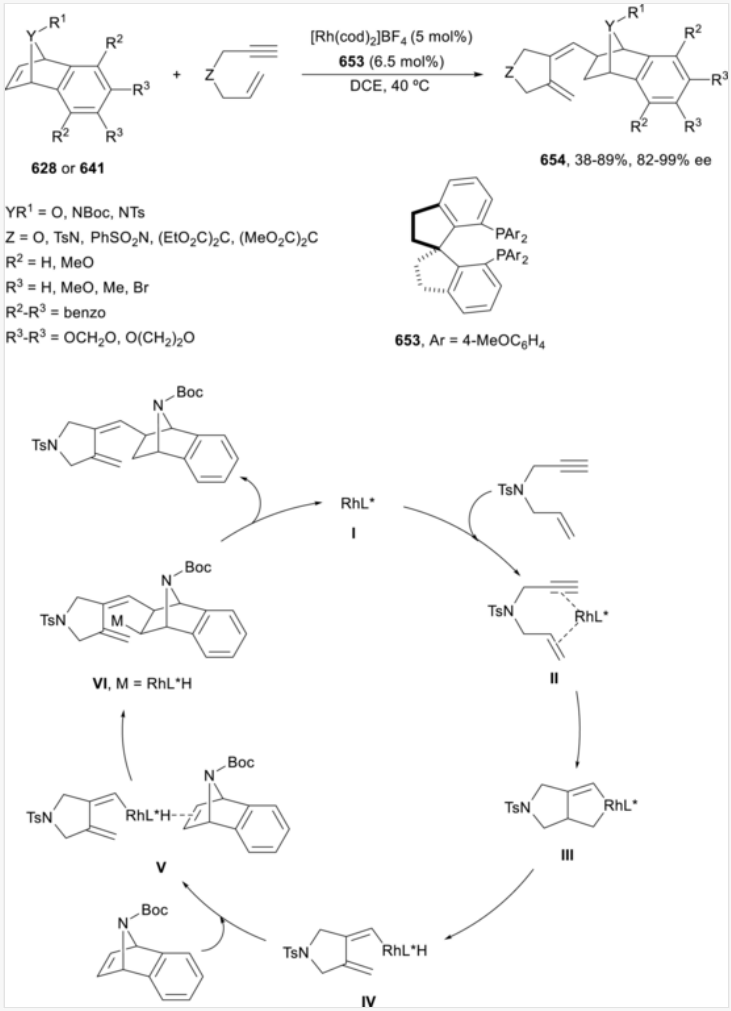


Rh-Catalyzed desymmetrization of *meso*-oxa- and azabenzonorbornadienes by an enantioselective Friedel-Crafts arylation ring opening with anilines.

The same group [366] has reported a Rh-catalyzed asymmetric cyclization-addition domino reaction of oxa- and azabenzonorbornadienes with 1,6-enynes. Using a spiro diphosphine (*R*)-An-SDP (**653**) as a chiral ligand highly enantioenriched products **654** were obtained in good yields and with excellent enantioselectivities (Scheme 208). In the proposed mechanism, the 1,6-enyne is coordinated by the catalyst **I** to form complex **II**, which is transformed into the rhodacyclopentene **III** by cycloisomerization. Then, β-hydride elimination generates the Rh hydride species **IV**, which coordinates the *N*-Boc-azabenzonorbornadiene to produce intermediate **V**. The alkene insertes into the Rh–C bond to give **VI**. By final exchange reaction of **VI** results product **654**.

alt-text: Scheme 208

Scheme 208

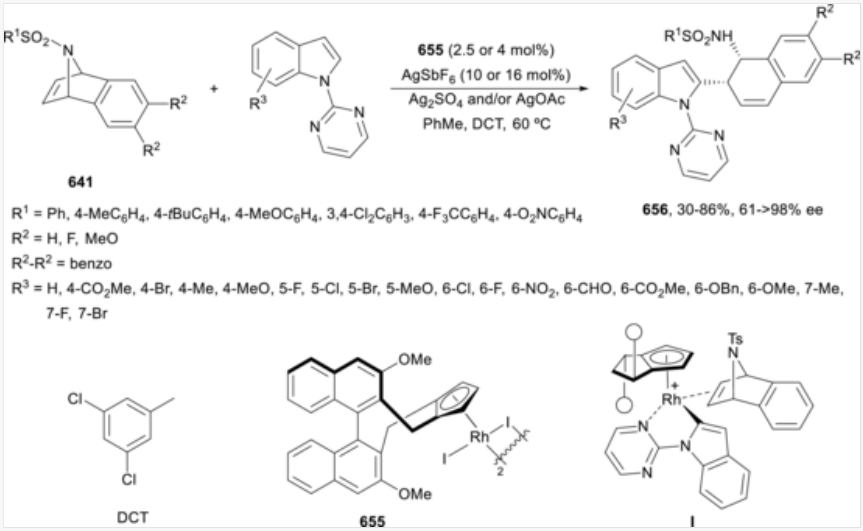


Rh-Catalyzed desymmetrization of *meso*-oxa and azabenzonorbornadienes by an enantioselective cyclization/addition reactions with 1,6-enynes.

Chiral Rh(III) complex **655** and $AgSbF_6$ catalyzed the enantioselective coupling of indoles and azabenzonorbornadienes **641** by C−H activation [367]. The corresponding *cis*-dihydronaphthylamines **656** were obtained in moderate to good yields and enantioselectivities (Scheme 209). $AgSbF_6$ activates Rh(III) acetate species suppressing the C3−H activation of indole. The mechanism of this reaction likely involves initial cyclometalation, enantioselective insertion of the olefin, illustrated in intermediate **I** and **II**, being intermediate **I** the most favorable, and final stereospecific β-nitrogen elimination.

alt-text: Scheme 209

Scheme 209



Rh-Catalyzed desymmetrization of *meso*-azabenzonorbornadienes **641** by an enantioselective coupling of índoles.

8.6 Diazanorbornenes

Desymmetrization of diazanorbornenes has been focused on metal-catalyzed ARO reactions by hydroboration, hydroformylation, dihydroxylation, arylation, etc. towards functionalized cyclopentenes and has been recently reviewed [368].

9 Conclusions

During the last five years, enantioselective desymmetrization has attracted the interest of many groups for the generation of optically active building blocks. Diarylmethanes and specially diarylmethylamines present in pharmaceutical compounds have been desymmetrized by Pd, Rh or Ir-catalyzed C–H activation reactions. Similarly, Pd-catalyzed C–H activation was also the best method for dibenzylmethylamines desymmetrization. Concerning desymmetrization of dienes and diynes, different transition metal-catalyzed processes have been used mainly in intramolecular transformations as well as organocatalyzed bromolactonizations. Acylation of 1,2-diols was carried out under metal- and organocatalyzed methods. In the case of 1,3-diols, many metal-catalyzed intramolecular alkylation, arylation and acylation methods have been developed. Acylation methods of 1,3-diols have been carried out also under organocatalyzed and mainly enzymatic processes. Alternatively, oxidation of acyclic and cyclic 1,3-diols can be performed using metal-catalyzed and enzymatic methodologies. Glycerol deivatives have ben mainly acylated or their esters hydrolyzed enzymatically. 4-Substituted cyclohexanones have been desymmetrized by transition metal-catalyzed α-cyclization reactions and by organocatalyzed aldol reactions, including Baeyer-Villiger organocatalyzed and enzymatic oxidations. Cyclic 1,3-diketones were enantioselectively cyclized under transition-metal-catalyzed conditions and by condensation using organocatalysts. Monoreduction reactions have been applied to cyclic 1,3-diketones by organocatalysis and enzymatic methods. Dicarboxylic acid derivatives were mainly desymmetrized by partial hydrolysis under organocatalysis or enzymatic catalysis. Diesters have been cyclized under Ni or Rh catalysis to β-ketoesters. Other strategies involved intramolecular lactonization and transesterification using organocatalysts. Cyclic anhydrides can be submitted to ring opening with alcohols using chiral bases or CPAs and under Rh or Ni catalytic addition of organometallic reagents to form ketoacids. Diamides were desymmetrized by enzymatic monoesterification and dinitriles under Ni catalysis gave β-ketonitriles. With respect to carbocycles, cyclopropanes were mainly enantioselectively functionalized by Pd-catalyzed arylation, borylation, carbonylation and vinylation involving C–H activation. Organocatalyzed processes took place under ring opening by chlorination or with carboxylic acids. Metal-catalyzed enantioselective additions of 3,3-disubstituted cyclopropenes to functionalized cyclopropanes have been extensively studied involving mainly carbometallation reactions. Four-membered compounds such as cyclobutanes and cyclobutanones have been desymmetrized by C–H activation under Ir or Pd-catalyzed borylation and arylation, whereas cyclobutenes underwent Cu-catalyzed enantioselective hydroborylation. Cyclopentanols underwent α-ketol rearrangement under Cu-catalyzed conditions. Substituted cyclopentenes have been mainly desymmetrized by enantioselective arylation under Pd-catalyzed Heck-Matsuda reaction as well as oxidative and reductive Heck reactions. Insertion of cyclopentenes and cyclohexanes tethered by a diazo compound has been performed under Rh- and Cu-catalyzed conditions, respectively. Cyclohexene derivatives can be also arylated under Pd-catalyzed Heck-

Matsuda reaction conditions and allylated by AAS. Small-ring heterocycles such as epoxides are generally desymmetrized by chiral Lewis acid catalyzed ring opening with heteronucleophiles and also with chiral Brønsted acid. Cyclopentene and cyclohexene oxides have been enzymatically hydrolytic desymmetrized by mutants limone epoxide hydrolases. Isomerization of cyclohexene oxide to the corresponding allylic alcohol has been recently performed by Ti/Co-cocatalyzed enantioselective radical redox-relay. Aziridines have been also desymmetrized by ring opening mainly under Mg-catalyzed conditions in the presence of different nucleophiles such as hydroxylamine derivatives, oxindoles, α,β-unsaturated γ-butyrolactam, naphthols, isocyanides, tetrazoles and pyrazoles. Oxa- and azabenzonorbornadienes were desymmetrized by asymmetric ring opening (ARO) or by addition to the C=C. Under Ir or Pd catalysis took place addition of thioles or diarylphosphines, respectively. However, azabenzonorbornadienes underwent ARO under Ir or Pd catalysis with carboxylic acids or boronic acids, respectively. Both bicycles reacted with anilines under Pd catalysis giving Friedel-Crafts products. In the case of Co-catalysis, alkylzinc halides reacted with oxabenzonorbornadienes by an ARO process and with azabenzonorbornadienes by addition to the double bond.

Q3 Uncited references

[59]; [72]; [130]; [200]; [357].

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

We thank the continuous financial support from the Spanish Ministerio de Economía y Competitividad (MINECO; project CTQ2016-81797-REDC, CTQ2017-85093-P), Ministerio de Ciencia, Innovación y Universidades (RED2018-102387-T, PID2019-107268 GB-100), FEDER, the Generalitat Valenciana (IDIFEDER/2021/013, Q2 CIDEGENT/2020/058), and the University of Alicante (VIGROB-068).

References

The corrections made in this section will be reviewed and approved by a journal production editor. The newly added/removed references and its citations will be reordered and rearranged by the production team.

[1] M.C. Willis, J. Chem. Soc., Perkin Trans. 1 (1999) 1765–1784.

[2] H. Wenemers, Chem. Commun. 47 (2011) 12036–12041.

[3] E. Garcia-Urdiales, I. Alonso, V. Gotor, Chem. Rev. 111 (2011) PR110-PR180.

[4] C.E. Müller, P.R. Schreiner, Angew. Chem. Int. Ed. 50 (2011) 6012–6042.

[5] M.D. Diaz de Villegas, J.A. Galvez, R. Badorrey, M.P. Lopez Ram de Viu, Chem. Eur J. 18 (2012) 13920–13935.

[6] H. Fernández-Pérez, P. Etayo, J.R. Lao, J.L. Núñez-Rico, A. Vidal-Ferran, Chem. Commun. 49 (2013) 10666–10675.

[7] G. Maertens, M.-A. Ménard, S. Casei, Synthesis 46 (2014) 1573–1582.

[8] K.A. Kalstabakken, A.M. Harned, Tetrahedron 70 (2014) 9571–9585.

[9] M. Wang, M. Feng, B. Tang, X. Jiang, Tetrahedron Lett. 55 (2014) 7147–7155.

[10] M.S. Manna, S. Mukherjee, Org. Biomol. Chem. 13 (2015) 18–24.

[11] K.S. Petersen, Tetrahedron Lett. 56 (2015) 6523–6535.

[12] L.W. Xu, Y. Chen, Y. Lu, Angew. Chem. Int. Ed. 54 (2015) 9456–9466.

[13] X.-P. Zeng, Z.-Y. Cao, Y.-H. Wang, F. Zhou, J. Zhou, Chem. Rev. 116 (2016) 7330–7396.

[14] A. Borissov, T.Q. Davies, S.R. Ellis, T.A. Fleming, M.S.W. Richardson, D.J. Dixon, Chem. Soc. Rev. 45 (2016) 5474–5540.

[15] M.A. Horwitz, J.S. Johnson, Eur. J. Org Chem. (2017) 1381–1390.

[16] T. Suzuki, Tetrahedron Lett. 58 (2017) 4731–4739.

[17] J. Merad, M. Candy, J.-M. Pons, C. Bressy, Synthesis 49 (2017) 1938–1954.

[18] D.A. Nagib, Angew. Chem. Int. Ed. 56 (2017) 7354–7356.

[19] R. Shintani, Synlett 29 (2018) 388–396.

[20] M. Inai, T. Asakawa, T. Kan, Tetrahedron Lett. 59 (2018) 1343–1347.

[21] Z. Wang, D. Pan, T. Li, Z. Jin, Chem. Asian J. 13 (2018) 2149–2163.

[22] D. Ameen, T.J. Snape, MedChemCommun 4 (2013) 893–915.

[23] A.J. Metrano, S.J. Miller, Acc. Chem. Res. 52 (2019) 199–215.

[24] C. de Risi, O. Bortolini, G. Di Carmine, D. Ragno, A. Massi, Synthesis 51 (2019) 1871–1891.

[25] A. Patti, C. Sanfilippo, Symmetry 12 (2020) 1454–1479.

[26] A.J. Metrano, A.J. Chinn, C.R. Shugrue, E.A. Stone, B. Kim, S.J. Miller, Chem. Rev. 120 (2020) 11479–11615.

[27] B. Kim, A.J. Chinn, D.R. Fandrick, C.H. Senanayake, R.A. Singer, S.J. Miller, J. Am. Chem. Soc. 138 (2016) 7939–7945.

[28] A.J. Chinn, B. Kim, Y. Kwon, S.J. Miller, J. Am. Chem. Soc. 139 (2017) 18107–18114.

[29] Y. Kwon, A.J. Chinn, B. Kim, S.J. Miller, Angew. Chem. Int. Ed. 57 (2018) 6251–6255.

[30] Y. Wang, C. Zheng, S.-L. You, Angew. Chem. Int. Ed. 56 (2017) 15093–15097.

[31] Y. Wang, W.-Y. Zhang, J.-H. Xie, Z.-L. Yu, J.-H. Tan, C. Zheng, X.-L. Hou, S.-L. You, J. Am. Chem. Soc. 142 (2020) 19354–19359.

[32] Y.-Y. Zhang, Y. Wei, M. Shi, Org. Lett. 21 (2019) 8250–8255.

[33] C. Nájera, I.P. Beletskaya, M. Yus, Chem. Soc. Rev. 48 (2019) 4515–4618.

[34] B. Li, Z. Chao, C. Li, Z. Gu, J. Am. Chem. Soc. 140 (2018) 9400–9403.

[35] Y.-L. Li, C. Zhang, X. Yin, X.-L. Yu, Z. Wang, H.-Z. Zhang, W.-Q. Yang, Synlett 31 (2020) 1077–1082.

[36] S. Li, X. Song, S.B. Poh, H. Yang, M.W. Wong, Y. Zhao, Chem. Eur J. 23 (2017) 2275–2281.

[37] S. Mondal, G. Panda, RSC Adv. 4 (2014) 28317–28358.

[38] S. Li, B. Liu, L. Chen, X. Li, J.-P. Cheng, Org. Chem. Front. 5 (2018) 1101–1107.

[39] J.T. Payne, P.H. Butkovich, Y. Gu, K.H. Kunze, H.J. Park, D.-S. Wang, J.C. Lewis, J. Am. Chem. Soc. 140 (2018) 546–549.

[40] C. Chen, Curr. Med. Chem. 15 (2008) 2173–2191.

[41] R. Basra, C. Kelleher, Therapeut. Clin. Risk Manag. 4 (2008) 117–128.

[42] M.D. Metcalf, A.S. Yekkirala, M.D. Powers, K.F. Kitto, C.A. Fairbanks, G.L. Wilcox, P.S. Portoghese, ACS Chem. Neurosci. 3 (2012) 505–509.

[43] A.E. Hurtley, E.A. Stone, A.J. Metrano, S.J. Miller, J. Org. Chem. 82 (2017) 11326–11336.

[44] I.P. Beletskaya, C. Nájera, M. Yus, Chem. Rev. 118 (2018) 5080–5200.

[45] D. Grosheva, N. Cramer, ACS Catal. 7 (2017) 7417–7420.

[46] L. Yang, M. Neuburger, O. Baudoin, Angew. Chem. Int. Ed. 57 (2018) 1394–1398.

[47] H. Shi, A.N. Herron, Y. Shao, Q. Shao, J.-Q. Yu, Nature 558 (2018) 581–585.

[48] D.E. Hill, J.-Q. Yu, D.G. Blackmond, J. Org. Chem. 85 (2020) 13674–13679.

[49] X.-F. Bai, Q.-C. Mu, Z. Xu, K.-F. Yang, L. Li, Z.-J. Zheng, C.-G. Xia, L.-W. Xu, ACS Catal. 9 (2019) 1431–1436.

[50] L. Lin, S. Fukagawa, D. Sekine, E. Tomita, T. Yoshino, S. Matsunaga, Angew. Chem. Int. Ed. 57 (2018) 12048–12052.

[51] X. Zou, H. Zhao, Y. Li, Q. Gao, Z. Ke, S. Xu, J. Am. Chem. Soc. 141 (2019) 5334–5342.

[52] G.R. Genov, J.L. Douthwaite, A.S.K. Lahdenperä, D.C. Gibson, R.J. Phipps, Science 367 (2020) 1246–1251.

[53] X. Vidal, J.L. Mascareñas, M. Gulías, J. Am. Chem. Soc. 141 (2019) 1862–1866.

[54] B. Su, T.-G. Zhou, X.-W. Li, X.-R. Shao, P.-L. Xu, W.-L. Wu, J.F. Hartwig, Z.-J. Shi, Angew. Chem. Int. Ed. 56 (2017) 1092–1096.

[55] B. Su, T.-G. Zhou, P.-L. Xu, Z.-J. Shi, J.F. Hartwig, Angew. Chem. Int. Ed. 56 (2017) 7205–7208.

[56] J. Luo, Q. Cao, X. Cao, X. Zhao, Nat. Commun. 9 (2018) 527.

[57] Q. Cao, J. Luo, X. Zhao, Angew. Chem. Int. Ed. 58 (2019) 1315–1319.

[58] F. Zhou, J. Liu, Q. Cai, Synlett 27 (2016) 664–675.

[59] F. Zhou, J. Guo, J. Liu, K. Ding, S. Yu, Q. Cai, J. Am. Chem. Soc. 134 (2012) 14326–14329.

[60] H. Han, T. Zhang, S.-D. Yang, Y. Lan, J.-B. Xia, Org. Lett. 21 (2019) 1749–1754.

[61] J. Wang, D.-W. Gao, J. Huang, S. Tang, Z. Xiong, H. Hu, S.-L. You, Q. Zhu, ACS Catal. 7 (2017) 3832–3836.

[62] Q. Ding, H. He, Q. Cai, Org. Lett. 20 (2018) 4554–4557.

[63] H. Fernández-Pérez, J.R. Lao, A. Vidal-Ferran, Org. Lett. 18 (2016) 2836–2839.

[64] T. Kang, K.L. White, T.J. Mann, A.H. Hoveyda, M. Movassaghi, Angew. Chem. Int. Ed. 56 (2017) 13857–13860.

[65] K.L. White, M. Movassaghi, J. Am. Chem. Soc. 138 (2016) 11383–11389.

[66] J.-W. Park, K.G.M. Kou, D.K. Kim, V.M. Dong, Chem. Sci. 6 (2015) 4479–4483.

[67] J.-W. Park, Z. Chen, V.M. Dong, J. Am. Chem. Soc. 138 (2016) 3310–3313.

[68] D.K. Kim, J. Riedel, R.S. Kim, V.M. Dong, J. Am. Chem. Soc. 139 (2017) 10208–10211.

[69] Q. Lin, Y. Li, D.K. Das, G. Zhang, Z. Zhao, S. Yang, X. Fang, Chem. Commun. 52 (2016) 6459–6462.

[70] U. Hennecke, M. Wilking, Synlett 25 (2014) 1633–1637.

[71] Y. Kawato, Y. Hamashima, Synlett 29 (2018) 1257–1271.

[72] Y. Nagao, T. Hisanaga, H. Egami, Y. Kawato, Y. Hamashima, Chem. Eur J. 23 (2017) 16758–16762.

[73] Y. Nagao, T. Hisanaga, T. Utsumi, H. Egami, Y. Kawato, Y. Hamashima, J. Org. Chem. 83 (2018) 7290–7295.

[74] M. Wilking, C.G. Daniliuc, U. Hennecke, Synlett 25 (2014) 1701–1704.

[75] Z.-L. Yu, Y.-F. Chen, N.-C. Jiang, J. Wang, L.-W. Fan, Y. Yuan, Z.-L. Li, Q.-S. Gu, X.-Y. Liu, Chem. Sci. 11 (2020) 5987–5993.

[76] M. Guerola, M. Escolano, G. Alzuet-Piña, E. Gómez-Bengoa, C. Ramírez de Arellano, M. Sánchez-Roselló, C. del Pozo, Org. Biomol. Chem. 16 (2018) 4650–4658.

[77] A. Studer, F. Schleth, Synlett (2005) 3033–3041.

[78] X. Bao, Q. Wang, J. Zhu, Angew. Chem. Int. Ed. 57 (2018) 1995–1999.

[79] K. Ohmi, Y. Miura, Y. Nakao, A. Goto, S. Yoshimura, H. Ouchi, M. Inai, T. Asakawa, F. Yoshimura, M. Kondo, T. Kan, Eur. J. Org Chem. (2020) 488–491.

[80] A. Goto, S. Yoshimura, Y. Nakao, M. Inai, T. Asakawa, M. Egi, T. Hamashima, M. Kondo, T. Kan, Org. Lett. 19 (2017) 3358–3361.

[81] D.W. Klasowski, S.F. Martin, Synlett 29 (2018) 430–432.

[82] D.H. Paull, C. Fang, J.R. Donald, A.D. Pansick, S.F. Martin, J. Am. Chem. Soc. 134 (2012) 11128–11131.

[83] E. Dolja, N. Funken, D. Slak, G. Schnakenburg, A. Gansäuer, ChemCatChem 11 (2019) 5421–5424.

[84] M. Spittler, K. Lutsenko, C. Czekelius, J. Org. Chem. 81 (2016) 6100–6105.

[85] C. Czekelius, Isr. J. Chem. 58 (2018) 1–11.

[86] A.K. Mourad, J. Leutzow, C. Czekelius, Angew. Chem. Int. Ed. 51 (2012) 11149–11152.

[87] F. Zhou, C. Tan, J. Tang, Y.-Y. Zhang, W.-M. Gao, H.-H. Wu, Y.-H. Yu, J. Zhou, J. Am. Chem. Soc. 135 (2013) 10994–10997.

[88] T. Song, L. Li, W. Zhou, Z.-J. Zheng, Y. Deng, Z. Xu, L.-W. Xu, Chem. Eur J. 21 (2015) 554–558.

[89] M.-Y. Chen, T. Song, Z.-J. Zheng, Z. Xu, Y.-M. Cui, L.-W. Xu, RSC Adv. 6 (2016) 58698–58708.

[90] M. Wilking, C. Muck-Lichtenfeld, C.G. Daniliuc, U. Hennecke, J. Am. Chem. Soc. 135 (2013) 8133–8136.

[91] M. Wilking, C.G. Daniliuc, U. Hennecke, Chem. Eur J. 22 (2016) 18601–18607.

[92] C. Fricke, M. Wilking, C.G. Daniliuc, U. Hennecke, Eur. J. Org Chem. (2018) 3158–3166.

[93] W. Luo, L. Lin, Y. Zhang, X. Liu, X. Fen, Org. Lett. 19 (2017) 3374–3377.

[94] S. Ma, Z. Lu, Angew. Chem. Int. Ed. 47 (2008) 258–297.

[95] S.S. Goh, S. Guduguntla, T. Kikuchi, M. Lutz, E. Otten, M. Fujita, B.L. Feringa, J. Am. Chem. Soc. 140 (2018) 7052–7055.

[96] N. Hamaguchi, M. Kuriyama, O. Onomura, Tetrahedron: Asymmetry 27 (2016) 177–181.

[97] R.-Z. Li, H. Tang, K.R. Yang, L.-Q. Wan, X. Zhang, J. Liu, Z. Fu, D. Niu, Angew. Chem. Int. Ed. 56 (2017) 7213–7217.

[98] Y. Hashimoto, C. Michimuko, K. Yamaguchi, M. Nakajima, M. Sugiura, J. Org. Chem. 84 (2019) 9313–9321.

[99] E. Chinnaraja, R. Arunachalam, J. Samanta, R. Natarajan, P.S. Subramanian, Appl. Organomet. Chem. (2019) e4827.

[100] R.A. Angnes, L.M. Thompson, M.S. Mashuta, C.R.D. Correia, G.B. Hammond, Adv. Synth. Catal. 360 (2018) 3760–3767.

[101] H. Mandai, K. Fujii, H. Yasuhara, K. Abe, K. Mitsudo, T. Korenaga, S. Suga, Nat. Commun. 7 (2016) 11297.

[102] H. Mandai, H. Yasuhara, K. Fujii, Y. Shimomura, K. Mitsudo, S. Suga, J. Org. Chem. 82 (2017) 6846–6856.

[103] Z. Cui, Y. Zhao, Y. Mao, T. Shi, L. Lu, H. Ma, Z. Wang, T. Chen, J. Chem. Technol. Biotechnol. 94 (2019) 2547–2554.

[104] B.M. Trost, D.J. Michaelis, S. Malhotra, Org. Lett. 15 (2013) 5274–5277.

[105] W. Lee, Asian J. Org. Chem. 8 (2019) 1687–1697.

[106] M. Shimizu, M. Mushika, I. Mizota, Y. Zhu, RSC Adv. 9 (2019) 23400–23407.

[107] M.S. Eno, A. Lu, J.P. Morten, J. Am. Chem. Soc. 138 (2016) 7824–7827.

[108] W. Yang, J. Yan, Y. Long, S. Zhang, J. Liu, Y. Zeng, Q. Cai, Org. Lett. 15 (2013) 6022–6025.

[109] J. Shi, T. Wang, Y. Huang, X. Zhang, Y.-D. Wu, Q. Cai, Org. Lett. 17 (2015) 840–843.

[110] W. Yang, Y. Liu, S. Zhang, Q. Cai, Angew. Chem. Int. Ed. 54 (2015) 8805–8808.

[111] Y. Zhang, Q. Wang, T. Wang, H. He, W. Yang, X. Zhang, Q. Cai, J. Org. Chem. 82 (2017) 1458–1463.

[112] Q.-Q. Zhou, F.-D. Lu, D. Liu, L.-Q. Lu, W.-J. Xiao, Org. Chem. Front. 5 (2018) 3098–3102.

[113] Y.-F. Cheng, J.-R. Liu, Q.-S. Gu, Z.-L. Yu, J. Wang, Z.-L. Li, J.-Q. Bian, H.-T. Wen, X.-J. Wang, X. Hong, X.-Y. Liu, Nat. Catal. 3 (2020) 401–410.

[114] K. Yamamoto, S. Ishimaru, T. Oyama, S. Tanigawa, M. Kuriyama, Org. Process Res. Dev. 23 (2019) 660–666.

[115] B. Hao, M.J. Gunaratna, M. Zhang, S. Weerasekara, S.N. Seiwald, V.T. Nguyen, A. Meier, D.H. Hua, J. Am. Chem. Soc. 138 (2016) 16839–16848.

[116] H. Mandai, K. Ashihara, K. Mitsudo, S. Suga, Chem. Lett. 47 (2018) 1360–1363.

[117] B.-S. Li, Y. Wang, R.S.J. Proctor, Z. Jin, Y.R. Chi, Chem. Commun. 52 (2016) 8313–8316.

[118] Z. Wu, J. Wang, ACS Catal. 7 (2017) 7647–7652.

[119] J.Y. See, H. Yang, Y. Zhao, M.W. Wong, Z. Ke, Y.-Y. Yeung, ACS Catal. 8 (2018) 850–858.

[120] C.D. Estrada, H.T. Ang, K.-M. Vetter, A.A. Ponich, D.G. Hall, J. Am. Chem. Soc. 143 (2021) 4162–4167.

[121] M. Kono, S. Harada, T. Nozaki, Y. Hashimoto, S. Murata, H. Gröger, Y. Kuroda, K. Yamada, K. Takasa, Y. Hamada, T. Nemoto, Org. Lett. 21 (2019) 3750–3754.

[122] A. Jadhav, W. Liang, P.C. Papageorgiou, A. Shoker, S.C. Kanthan, J. Balsevich, A.S. Levy, S. Heximer, P.H. Backx, V. Gopalakrishnan, J. Pharmacol. Exp. Therapeut. 345 (2013) 383–392.

[123] L. Moisan, P. Thuery, M. Nicolas, E. Doris, B. Rousseau, Angew. Chem. Int. Ed. 45 (2006) 5334–5336.

[124] S.-S. Meng, Y. Liang, K.-S. Cao, L. Zou, X.-B. Lin, H. Yang, K.N. Houk, W.-H. Zheng, J. Am. Chem. Soc. 136 (2014) 12249–12252.

[125] S.-S. Meng, W.-B. Tang, W.H. Zheng, Org. Lett. 20 (2018) 518–521.

[126] S.-S. Meng, P. Yu, Y.-Z. Yu, Y. Liang, K.N. Houk, W.-H. Zheng, J. Am. Chem. Soc. 142 (2020) 8506–8513.

[127] M. Kawasaki, M. Shimizu, S. Kuroyanagi, Y. Shishido, T. Komiyama, N. Toyooka, Tetrahedron: Asymmetry 27 (2016) 285–293.

[128] R. Kolodziesjska, M. Kwit, R. Studzińska, M. Jelecki, J. Mol. Catal. B Enzym. 133 (2016) 98–106.

[129] R. Kolodziejska, R. Studzinska, H. Pawluk, Chirality (2017) 1–9.

[130] B.T. Khong, V.S. Pamarthy, T. Gallagher, Z.M.A. Judeh, Eur. J. Org Chem. (2016) 3084–3089.

[131] Y. Tokairin, H. Konno, Tetrahedron 73 (2017) 39–45.

[132] E. Brenna, F. Cannavale, M. Crotti, V. De Vitis, F.G. Gath, G. Migliazza, F. Molinari, F. Parmeggiani, D. Romano, S. Santangelo, ChemCatChem 8 (2016) 3796–3803.

[133] V. De Vitis, F. Dall'Oglio, A. Pinto, C. De Micheli, F. Molinari, P. Conti, D. Romano, L. Tamborini, Chemistry Open 6 (2017) 668–673.

[134] J. Hinze, P. Süss, S. Strohmaler, U.T. Bornscheuer, R. Wardenga, J. von Langermann, Org. Process Res. Dev. 20 (2016) 1258–1264.

[135] S. Putta, A.M. Reddy, G. Sheelu, B.V. Subba Reddy, T. Kumaraguru, Tetrahedron 74 (2018) 6673–6679.

[136] C. Holec, D. Sandkuhl, D. Rother, W. Kroutil, J. Pietruszka, ChemCatChem 7 (2015) 3125–3130.

[137] C. Holec, K. Neufeld, J. Pietruszka, Adv. Synth. Catal. 358 (2016) 1810–1819.

[138] K.N. Gavrilov, I.S. Mikhel, I.V. Chuchelkin, S.V. Zheglov, V.K. Gavrilov, K.P. Birin, V.A. Tafeenko, V.V. Chemyshev, N.S. Goulioukina, I.P. Beletskaya, ChemistrySelect 1 (2016) 4173–4186.

[139] K.N. Gavrilov, I.S. Mikhel, S.V. Zheglov, V.K. Gavrilov, I.V. Chuchelkin, I.D. Firsin, K.P. Birin, I.S. Pytskii, K.A. Paseshnichenko, V.A. Tafeenko, V.V. Chernyshev, A.A. Shiryaev, Org. Chem. Front. 6 (2019) 1637–1648.

[140] R. Jacques, R.D.C. Pullin, S.P. Fletcher, Nat. Commun. 10 (2019) 21.

[141] R. Jacques, A.M.L. Hell, R.D.C. Pullin, S.P. Fletcher, Tetrahedron 75 (2019) 130560.

[142] K. Xu, Y. Zheng, Y. Ye, D. Liu, W. Zhang, Org. Lett. 22 (2020) 8836–8841.

[143] A.K. Ghosh, A. Sarkar, Eur. J. Org Chem. (2016) 6001–6009.

[144] A.K. Ghosh, X. Xu, Org. Lett. 6 (2004) 2055–2058.

[145] V.K. Mishra, P.C. Ravikumar, M.E. Maier, J. Org. Chem. 81 (2016) 9728–9737.

[146] K. Muralikrishna, V. Satyanarayana, G.C. Kumar, J.S. Yadav, ChemistrySelect 4 (2019) 3002–3005.

[147] E. Martínez-Rojas, T. Olejniczak, K. Neumann, L.-A. Garbe, F. Boratynski, Chirality 28 (2016) 623–627.

[148] L. Moni, L. Banfi, D. Cartagenova, A. Cavalli, C. Lambruschini, E. Martino, R.V.A. Orru, E. Ruijter, J.M. Saya, J. Sgrignani, R. Riva, Org. Chem. 7 (2020) 380–398.

[149] G. Yu, B. Jung, S. Lim, H.-S. Lee, S.H. Kang, Asian J. Org. Chem. 5 (2016) 107–113.

[150] K. Yamamoto, Y. Tsuda, M. Kuriyama, Y. Demizu, O. Onamura, Chem. Asian J. 15 (2020) 840–844.

[151] G. Tangherlini, T. Torregrosa, O. Agoglitta, J. Köhler, J. Melesina, W. Sippl, R. Holl, Bioorg. Med. Chem. 24 (2016) 1032–1044.

[152] M. McLaughlin, J. Kong, K.M. Belyk, B. Chen, A.W. Gibson, S.P. Keen, D.R. Lieberman, E.M. Milczek, J.C. Moore, D. Murray, F. Peng, J. Qi, R.A. Reamer, Z.J. Song, L. Tan, L. Wang, M.J. Williams, Org. Lett. 19 (2017) 926–929.

[153] T. González-García, A. Verstuyf, L. Verlinden, S. Fernández, M. Ferrero, Adv. Synth. Catal. 360 (2018) 2762–2772.

[154] H. Yang, K.-S. Cao, W.-H. Zheng, Chem. Commun. 53 (2017) 3737–3740.

[155] M.F.P. Ribeiro, K.C. Pais, B.S.M. de Jesus, R. Fernanedz-Lafuente, D.M.G. Freire, E.A. Manoel, A.B.C. Simas, Eur. J. Org Chem. (2018) 386–391.

[156] J. Sietmann, J.M. Wiest, Angew. Chem. Int. Ed. 59 (2020) 6964–6974.

[157] R. Manzano, S. Datta, R.S. Paton, D.J. Dixon, Angew. Chem. Int. Ed. 56 (2017) 5834–5838.

[158] L. Zhang, K. Yamazaki, J.A. Leitch, R. Manzano, V.A.M. Atkinson, T.A. Hamlin, D.J. Dixon, Chem. Sci. 11 (2020) 7444–7450.

[159] R.-R. Liu, B.-L. Li, J. Lu, C. Chen, J.-R. Gao, Y.-X. Jia, J. Am. Chem. Soc. 138 (2016) 5198–5201.

[160] Q. Wei, J. Cai, X.-D. Hu, J. Chao, H. Cong, C. Zheng, W.-B. Liu, ACS Catal. 10 (2020) 216–224.

[161] H.-C. Shen, L. Zhang, S.-S. Chen, J. Feng, B.-W. Zhang, Y. Zhang, X. Zhang, Y.-D. Wu, L.-Z. Gong, ACS Catal. 9 (2019) 791–797.

[162] S.K. Nimmagadda, S.C. Mallojjala, L. Woztas, S.E. Wheeler, J.C. Antilla, Angew. Chem. Int. Ed. 56 (2017) 2454–2458.

[163] W. Wu, W. Cao, L. Hu, Z. Su, X. Liu, X. Feng, Chem. Sci. 10 (2019) 7003–7008.

[164] D.B. Ramachary, K.S. Shruthi, J. Org. Chem. 81 (2016) 2405–2419.

[165] T.C. Nugent, F.T. Najafian, H.A.E.D. Hussein, I. Hussain, Chem.−Eur. J. 22 (2016) 14342–14348.

[166] T.C. Nugent, P. Spiteller, I. Hussain, H.A.E.D. Hussein, F.T. Najafian, Adv. Synth. Catal. 358 (2016) 3706–3713.

[167] H. Zhou, H.Y. Bae, M. Leutzsch, J.L. Kennemur, D. Bécart, B. List, J. Am. Chem. Soc. 142 (2020) 13695–13700.

[168] L. Zhu, L. Zhang, S. Luo, Angew. Chem. Int. Ed. 57 (2018) 2253–2258.

[169] M. Cortigiani, A. Mereu, M.G. Healy, M.F.A. Adamo, J. Org. Chem. 84 (2019) 4112–4119.

[170] B.-L. Li, W.-Y. Gao, S.-Q. Zhang, X.-Q. Han, J. Lu, R.-X. Liang, X. Hong, Y.X. Jia, Chin. J. Org. Chem. 37 (2019) 63–70.

[171] G. Li, M.J.L.J. Fürst, H.R. Mansouri, A.K. Ressmann, A. Ilie, F. Rudroff, M.D. Mihovilovic, M.W. Fraaije, M.T. Reetz, Org. Biomol. Chem. 15 (2017) 9824–9829.

[172] T.H. Al-Tel, V. Srinivasulu, M. Ramanathan, N.C. Soares, A. Sebastian, M.L. Bolognesi, I.A. Abu-Yousef, A. Majdalawieh, Org. Biomol. Chem. 18 (2020) 8526–8571.

[173] G. Chandra, S. Patel, ChemistrySelect 5 (2020) 12885–12909.

[174] B. Chen, C.-Y. He, W.-D. Chu, Q.-Z. Liu, Org. Chem. Front. 8 (2021) 825–843.

[175] Y.-X. Ding, Z.-H. Zhu, C.-B. Yu, Y.-G. Zhou, Asian J. Org. Chem. 9 (2020) 1942–1952.

[176] H. Hagiwara, Nat. Prod. Commun. 15 (2020) 1–17.

[177] C. Zhu, D. Wang, Y. Zhao, W.-Y. Sun, Z. Shi, J. Am. Chem. Soc. 139 (2017) 16486–16489.

[178] J. Cai, Q. Wei, X.-D. Hu, Y. Zhang, W. Li, H. Cong, W. Liu, W.-B. Liu, Synthesis 50 (2018) 1661–1666.

[179] P. Zhou, T. Xu, Chem. Commun. 56 (2020) 8194–8197.

[180] C. Clarke, C.A. Incerti-Pradillos, H.W. Lam, J. Am. Chem. Soc. 138 (2016) 8068–8071.

[181] J.M. Zanghi, S. Liu, S.J. Meek, Org. Lett. 21 (2019) 5172–5177.

[182] A. Selmani, S. Darses, Org. Lett. 22 (2020) 2681–2686.

[183] P. Zheng, X. Han, J. Hu, X. Zhao, T. Xu, Org. Lett. 21 (2019) 6040–6044.

[184] B. Bradshaw, J. Bonjoch, Synlett 23 (2012) 337–356.

[185] Y. Kawamoto, D. Ozone, T. Kobayashi, H. Ito, Eur. J. Org Chem. (2020) 4050–4058.

[186] S. Shee, S. Mukherjee, R.G. Gonnade, A.T. Biju, Org. Lett. 22 (2020) 5407–5411.

[187] K.-G. Wen, C. Liu, D.-H. Wei, Y.-F. Niu, Y.-Y. Peng, X.-P. Zeng, Org. Lett. 23 (2021) 1118–1122.

[188] B. Yang, J. Dai, Y. Luo, K.K. Lau, Y. Lan, Z. Shao, Y. Zhao, J. Am. Chem. Soc. 143 (2021) 4179–4186.

[189] S. Müller, M.J. Webber, B. List, J. Am. Chem. Soc. 133 (2011) 18534–18537.

[190] B. Ghosh, R. Balhara, G. Jindal, S. Mukherjee, Angew. Chem. Int. Ed. 60 (2021) 9086–9092.

[191] X.-L. Qin, A. Li, F.-S. Han, J. Am. Chem. Soc. 143 (2021) 2994–3002.

[192] T. Sugai, S. Higashibayashi, K. Hanaya, Tetrahedron 74 (2018) 3469–3487.

[193] B.-C. Cao, G.-J. Wu, F. Yu, Y.-P. He, F.-S. Han, Org. Lett. 20 (2018) 3687–3690.

[194] G.-J. Wu, Y.-H. Zhang, D.-X. Tan, L. He, B.-C. Cao, Y.-P. He, F.-S. Han, J. Org. Chem. 84 (2019) 3223–3238.

[195] X. Chen, H. Zhang, M.A. Maria-Solano, W. Liu, J. Li, J. Feng, X. Liu, S. Osuna, R.-T. Guo, Q. Wu, D. Zhu, Y. Ma, Nat. Catal 2 (2019) 931–941.

[196] J. Li, J. Feng, X. Chen, J. Gong, Y. Cui, H. Zhang, D. Bu, Q. Wu, D. Zhu, Org. Lett. 22 (2020) 3444–3448.

[197] T. Honna, K. Fuhshuku, Mol. Catal. 497 (2020) 111217.

[198] T. Das, ChemistrySelect 5 (2020) 14484–14509.

[199] C.-B. Yu, H.-D. Wang, B. Song, H.-Q. Shen, J.-J. Fan, Y.-G. Zhou, Sci. China Chem. 63 (2020) 215–221.

[200] H. Wang, Y. Zhao, Y.-X. Ding, C.-B. Yu, Y.-G. Zhou, Asian J. Org. Chem. 9 (2020) 753–756.

[201] J.A. Enquist Jr., B.M. Stoltz, Nature 453 (2008) 1228–1231.

[202] K.E. Kim, B.M. Stoltz, Org. Lett. 18 (2016) 5720–5723.

[203] R. Sarkar, S. Mukherjee, Org. Lett. 18 (2016) 6160–6163.

[204] M.S. Manna, S. Mukherjee, J. Am. Chem. Soc. 137 (2015) 130–133.

[205] C.J.C. Lamb, F. Vilela, A.-L. Lee, Org. Lett. 21 (2019) 8689–8694.

[206] Y. Hong, J. Chen, Z. Zhang, Y. Liu, W. Zhang, Org. Lett. 18 (2016) 2640–2643.

[207] J. Zhou, V. Wakchaure, P. Kraft, B. List, Angew. Chem. Int. Ed. 47 (2008) 7656–7658.

[208] Y.-F. Zhang, S.-J. Yin, M. Zhao, J.-Q. Zhang, H.-Y. Li, X.-W. Wang, RSC Adv. 6 (2016) 30683–30689.

[209] B.-B. Sun, Y.-F. Zhang, J.-Q. Zhang, S.-J. Yin, W.-T. Fan, H.-Y. Li, X.-W. Wang, Eur. J. Org Chem. (2017) 2871–2877.

[210] Y. Kurimoto, T. Nasu, Y. Fujii, K. Asano, S. Matsubara, Org. Lett. 21 (2019) 2156–2160.

[211] S.N. Karad, H. Panchal, C. Clarke, W. Lewis, H.W. Lam, Angew. Chem. Int. Ed. 57 (2018) 9122–9125.

[212] A. Selmani, S. Darses, Org. Lett. 21 (2019) 8122–8126.

[213] J.E. Wilent, K.S. Petersen, J. Org. Chem. 79 (2014) 2303–2307.

[214] J.E. Wilent, K.S. Petersen, Org. Synth. 93 (2016) 75–87.

[215] A.M. Kelley, E. Minerali, J.E. Wilent, N.J. Chambers, K.J. Stingley, G.T. Wilson, K.S. Petersen, Tetrahedron Lett. 60 (2019) 1262–1264.

[216] A.M. Kelley, R.D. Haywood, J.C. White, K.S. Petersen, ChemistrySelect 5 (2020) 3018–3022.

[217] A. Puglisi, C. Giustini, A. Ricucci, E. Perotti, L. Massaro, D. Morra, F. Ciucci, A. Zucchet, A. Antenucci, M. Moliterno, S. Placidi, F. Sciubba, L. Galantini, R. Salvio, M. Bella, Chem. Eur J. 24 (2018) 6941–6945.

[218] P. Süss, S. Illner, J. von Langermann, S. Borchert, U.T. Bornscheuer, R. Wardenga, U. Kragl, Org. Process Res. Dev. 18 (2014) 897–903.

[219] P. Süss, S. Borchert, J. Hinze, S. Illner, J. von Langermann, U. Kragl, U.T. Bornscheuer, R. Wardenga, Org. Process Res. Dev. 19 (2015) 2034–2038.

[220] M.P. Meissner, P. Süss, H. Brundiek, J.M. Woodley, J. von Langermann, Org. Process Res. Dev. 22 (2018) 1518–1523.

[221] M. Häfner, Y.M. Sokolenko, P. Gamerdinger, E. Stempel, T. Gaich, Org. Lett. 21 (2019) 7370–7374.

[222] P. Walser, P. Renold, V. N'Goka, F. Hosseinzadeh, C. Tamm, Helv. Chim. Acta 74 (1991) 1941–1952.

[223] J. Liang, J.E. Cochran, W.A. Dorsch, I. Davies, M.P. Clark, Org. Process Res. Dev. 20 (2016) 965–969.

[224] P. Spránitz, P. Söregl, B.B. Botlik, M. Berta, T. Soós, Synthesis 51 (2019) 1263–1272.

[225] W.D. Mackay, J.S. Johnson, Org. Lett. 18 (2016) 536–539.

[226] C. Bolm, I. Schiffers, I. Atodiresu, C.P.R. Hackenberger, Tetrahedron: Asymmetry 14 (2003) 3455–3467.

[227] S.H. Oh, H.S. Rho, J.W. Lee, J.E. Lee, S.H. Youk, J. Chin, C.E. Song, Angew. Chem. Int. Ed. 47 (2008) 7872–7875.

[228] S.E. Park, E.H. Nam, H.B. Jang, J.S. Oh, S. Some, Y.S. Lee, C.E. Song, Adv. Synth. Catal. 352 (2010) 2211–2217.

[229] K. Blise, M.W. Cvitkovic, N.J. Gibbs, S.F. Roberts, R.M. Whitaker, G.E. Hofmeister, D. Kohen, J. Org. Chem. 82 (2017) 1347–1355.

[230] S. Takata, Y. Endo, M.S. Ullah, S. Itsuno, RSC Adv. 6 (2016) 72300–72305.

[231] R. Borrmann, V. Palchyk, A. Pick, M. Rueping, ACS Catal. 8 (2018) 7991–7996.

[232] C. Rizzo, A. Mandoli, S. Marullo, F. D'Anna, J. Org. Chem. 84 (2019) 6356–6365.

[233] L.-J. Yan, H.-F. Wang, W.-X. Chen, Y. Tao, K.-J. Jin, F.-E. Chen, ChemCatChem (2016) 2249–2253.

[234] R. Craig, M. Litvajova, S.A. Cronin, S.J. Connon, Chem. Commun. 54 (2018) 10108–10111.

[235]

K. Yamada, A. Oonishi, Y. Kuroda, S. Harada, H. Kiyama, Y. Yamaoka, K. Takasu, Tetrahedron Lett. 57 (2016) 4098–4100.

[236] M.J. Cook, T. Rovis, J. Am. Chem. Soc. 129 (2007) 9302–9303.

[237] A.K. Ghosh, K. Lv, N. Ma, E.L. Cárdenas, K.A. Effenberger, M.S. Jurica, Org. Biomol. Chem. 14 (2016) 5263–5271.

[238] E.E. Stache, T. Rovis, A.G. Doyle, Angew. Chem. Int. Ed. 56 (2017) 3679–3683.

[239] O. Gutierrez, J.C. Tellis, D.N. Primer, G.A. Molander, M.C. Kozlowski, J. Am. Chem. Soc. 137 (2015) 4896–4899.

[240] J.-J. Zhao, S. Yu, Synlett 32 (2021) 391–394.

[241] P.-H. Chan, S.-W. Tsai, Chem. Eng. Sci. 139 (2016) 41–48.

[242] T.-Y. Wu, Y.-R. Lai, S.-W. Tsai, Appl. Biochem. Biotechnol. 105 (2017) 578–592.

[243] Y.-F. Ao, L.-B. Zhang, Q.-Q. Wang, D.-X. Wang, M.-X. Wang, Adv. Synth. Catal. 360 (2018) 4594–4603.

[244] H.-J. Hu, P. Chen, Y.-F. Ao, Q.-Q. Wang, D.-X. Wang, M.-X. Wang, Org. Chem. Front. 6 (2019) 808–812.

[245] Z. Lu, X.-D. Hu, H. Zhang, X.-W. Zhang, J. Cai, M. Usman, H. Cong, W.-B. Liu, J. Am. Chem. Soc. 142 (2020) 7328–7333.

[246] H. Mei, L. Lin, B. Shen, X. Liu, X. Feng, Org. Chem. Front. 5 (2018) 2505–2509.

[247] C.L. Ladd, A.B. Charette, Org. Lett. 18 (2016) 6046–6049.

[248] C. Mayer, C.L. Ladd, A.B. Charette, Org. Lett. 21 (2019) 2639–2644.

[249] N.C. Bruno, N. Niljianskul, S.L. Buchwald, J. Org. Chem. 79 (2014) 4161–4166.

[250] T. Lee, J.F. Hartwig, Angew. Chem. Int. Ed. 55 (2016) 8723–8728.

[251] J. He, Q. Shao, Q. Wu, J.-Q. Yu, J. Am. Chem. Soc. 139 (2017) 3344–3347.

[252] Y. Shi, Q. Gao, S. Xu, J. Am. Chem. Soc. 141 (2019) 10599–10604.

[253] P.-X. Shen, L. Hu, Q. Shao, K. Hong, J.-Q. Yu, J. Am. Chem. Soc. 140 (2018) 6545–6549.

[254] L. Hu, P.-X. Shen, Q. Shao, K. Hong, J.X. Qiao, J.-Q. Yu, Angew. Chem. Int. Ed. 58 (2019) 2134–2138.

[255] Z. Zhuang, J.-Q. Yu, J. Am. Chem. Soc. 142 (2020) 12015–12019.

[256] D. Perrotta, M.-M. Wang, J. Waser, Angew. Chem. Int. Ed. 57 (2018) 5120–5123.

[257] J. Wallbaum, L.K.B. Garve, P.G. Jones, D.B. Werz, Chem. Eur J. 22 (2016) 18756–18759.

[258] C. Sparr, R. Gilmour, Angew. Chem. Int. Ed. 50 (2011) 8391–8395.

[259] E. Diaz, E. Reyes, U. Uria, L. Carrillo, T. Tejero, P. Merino, J.L. Vicario, Chem. Eur J. 24 (2018) 8764–8768.

[260] H.-L. Teng, Y. Luo, B. Wang, L. Zhang, M. Nishiura, Z. Hou, Angew. Chem. Int. Ed. 55 (2016) 15406–15410.

[261] Z. Li, J. Zhao, B. Sun, T. Zhou, M. Liu, S. Liu, M. Zhang, Q. Zhang, J. Am. Chem. Soc. 139 (2017) 11702–11705.

[262] M. Rubina, M. Rubin, V. Gevorgyan, J. Am. Chem. Soc. 125 (2003) 7198–7199.

[263] A. Edwards, M. Rubina, M. Rubin, Chem. Eur J. 24 (2018) 1394–1403.

[264] M. Rubina, M. Rubin, V. Gevorgyan, J. Am. Chem. Soc. 126 (2004) 3688–3689.

[265] Z.-Y. Zhao, Y.-Y. Nie, R.-H. Tang, G.-W. Yin, J. Cao, Z. Xu, Y.-M. Cui, Z.-J. Zheng, L.-W. Xu, ACS Catal. 9 (2019) 9110–9116.

[266] L. Dian, I. Marek, Angew. Chem. Int. Ed. 57 (2018) 3682–3686.

[267] D.S. Muller, I. Marek, J. Am. Chem. Soc. 137 (2015) 15414–15417.

[268] D.S. Muller, I. Marek, Chem. Soc. Rev. 45 (2016) 4552–4566.

[269] L. Dian, D.S. Müller, I. Marek, Angew. Chem. Int. Ed. 56 (2017) 6783–6787.

[270] M. Simaan, I. Marek, Angew. Chem. Int. Ed. 57 (2018) 1543–1546.

[271] H. Sommer, I. Marek, Chem. Sci. 9 (2018) 6503–6508.

[272] H. Li, M. Zhang, H. Mehfooz, D. Zhu, J. Zhao, Q. Zhang, Org. Chem. Front. 6 (2019) 3387–3391.

[273] Z. Li, M. Zhang, Y. Zhang, S. Liu, J. Zhao, Q. Zhang, Org. Lett. 21 (2019) 5432–5437.

[274] Y. Luo, H.-L. Teng, M. Nishiura, Z. Hou, Angew. Chem. Int. Ed. 56 (2017) 9207–9210.

[275] H.-L. Teng, Y. Ma, G. Zhan, M. Nishiura, Z. Hou, ACS Catal. 8 (2018) 4705–4709.

[276] H.-L. Teng, Y. Luo, M. Nishiura, Z. Hou, J. Am. Chem. Soc. 139 (2017) 16506–16509.

[277] M. Wang, P. Lu, Org. Chem. Front. 5 (2018) 254–259.

[278] J. Li, K. Gao, M. Bian, H. Ding, Org. Chem. Front. 7 (2020) 136–154.

[279] K.-G. Wen, Y.-Y. Peng, X.-P. Zeng, Org. Chem. Front. 7 (2020) 2576–2597.

[280] K.-J. Xiao, D.W. Lin, M. Miura, R.-Y. Zhu, W. Gong, M. Wasa, J.-Q. Yu, J. Am. Chem. Soc. 136 (2014) 8138–8142.

[281] X. Chen, L. Chen, H. Zhao, Q. Gao, Z. Shen, S. Xu, Chin. J. Chem. 38 (2020) 1533–1537.

[282] L.-J. Xiao, K. Hong, F. Luo, L. Hu, W.R. Ewing, K.-S. Yeung, J.-Q. Yu, Angew. Chem. Int. Ed. 59 (2020) 9594–9600.

[283] F. Ratsch, W. Schlundt, D. Albat, A. Zimmer, J.-M. Neudörfl, T. Netscher, H.-G. Schmalz, Chem. Eur J. 25 (2019) 4941–4945.

[284] F. Ratsch, J.P. Strache, W. Schlundt, J.-M. Neudörfl, A. Adler, S. Aziz, B. Goldfuss, H.-G. Schmalz, Chem. Eur J. 27 (2021) 4640–4651.

[285] T. Seiser, N. Cramer, J. Am. Chem. Soc. 132 (2010) 5340–5341.

[286] S. Xu, Z. Wang, X. Zhang, X. Zhang, K. Ding, Angew. Chem. Int. Ed. 47 (2008) 2840–2843.

[287] M. Wang, J. Chen, Z. Chen, C. Zhong, P. Lu, Angew. Chem. Int. Ed. 57 (2018) 2707–2711.

[288] A. Parra, L. Amenós, M. Guisán-Ceinos, A. López, J.L. García-Ruano, M. Tortosa, J. Am. Chem. Soc. 136 (2014) 15833–15836.

[289] M. Guisán-Ceinos, A. Parra, V. Martín-Heras, M. Tortosa, Angew. Chem. Int. Ed. 55 (2016) 6969–6972.

[290] H. Wu, R. Andres, Q. Wang, J. Zhu, Angew. Chem. Int. Ed. 58 (2019) 499–503.

[291] C.R.D. Correia, C.C. Oliveira, A.G. Salles Jr., E.A.F. Santos, Tetrahedron Lett. 53 (2012) 3325–3328.

[292] C.M. Avila, J.S. Patel, Y. Reddi, M. Saito, H.M. Nelson, H.P. Shunatona, M.S. Sigman, R.B. Sunoj, F.D. Toste, Angew. Chem. Int. Ed. 56 (2017) 5806–5811.

[293] Y. Reddi, C.C. Tsai, C.M. Avila, F.D. Toste, R.B. Sunoj, J. Am. Chem. Soc. 141 (2019) 998–1009.

[294] R.A. Angnes, J.M. Oliveira, C.C. Oliveira, N.C. Martins, C.R.D. Correia, Chem. Eur J. 20 (2014) 13117–13121.

[295] J.O. Silva, R.A. Angnes, V.H. Menezes da Silva, B.M. Servilha, M. Adeel, A.A.C. Braga, A. Aponic, C.R.D. Correia, J. Org. Chem. 81 (2016) 2010–2018.

[296] J.M. Oliveira, R.A. Angnes, I.U. Khan, E.C. Polo, G. Heerdt, B.M. Servilha, V.H. Menezes da Silva, A.A.C. Braga, C.R.D. Correia, Chem. Eur J. 24 (2018) 11738–11747.

[297] I.U. Khan, S. Kattela, A. Hassan, C.R.D. Correia, Org. Biomol. Chem. 14 (2016) 9476–9480.

[298] S. Kattela, G. Heerdt, C.R.D. Correia, Adv. Synth. Catal. 359 (2017) 260–267.

[299] V.C. Oliveira, J.M. Oliveira, V.H. Menezes da Silva, I.U. Khan, C.R.D. Correia, Adv. Synth. Catal. 362 (2020) 3395–3406.

[300] G. Chen, J. Cao, Q. Wang, J. Zhu, Org. Lett. 22 (2020) 322–325.

[301] Z. Yuan, Z. Feng, Y. Feng, X. Zhao, A. Lin, H. Yao, Angew. Chem. Int. Ed. 58 (2019) 2884–2885.

[302] Z. Yuan, Y. Zeng, Z. Feng, Z. Guan, A. Lin, H. Yao, Nat. Commun. 11 (2020) 2544.

[303] T. Miyazawa, K. Minami, M. Ito, M. Anada, S. Matsunaga, S. Hashimoto, Tetrahedron 72 (2016) 3939–3947.

[304] W.M. Sherrill, M. Rubin, J. Am. Chem. Soc. 130 (2008) 13804–13809.

[305] C. You, B. Wei, X. Li, Y. Yang, Y. Liu, H. Lv, X. Zhang, Angew. Chem. Int. Ed. 55 (2016) 6511–6514.

[306] H. Wu, Q. Wang, J. Zhu, Angew. Chem. Int. Ed. 57 (2018) 2721–2725.

[307] M.T. Knowe, M.W. Danneman, S. Sun, M. Pink, J.N. Johnston, J. Am. Chem. Soc. 140 (2018) 1998–2001.

[308] T.A. Brouder, C.N. Slattery, A. Ford, U.B.R. Khandavilli, E. Skořepová, K.S. Eccles, M. Lusi, S.E. Lawrence, A.R. Maguire, J. Org. Chem. 84 (2019) 7543–7563.

[309] Q. An, D. Liu, J. Shen, Y. Liu, W. Zhang, Org. Lett. 19 (2017) 238–241.

[310] K. Xu, H. Liu, Y. Hou, J. Shen, D. Liu, W. Zhang, Chem. Commun. 55 (2019) 13295–13298.

[311] K. Xu, J. Ye, H. Liu, J. Shen, D. Liu, W. Zhang, Adv. Synth. Catal. 362 (2020) 2059–2069.

[312] E. Picazo, L.A. Morrill, R.B. Susick, J. Moreno, J.M. Smith, N.K. Garg, J. Am. Chem. Soc. 140 (2018) 6483–6492.

[313] M. Inai, T. Asakawa, T. Kan, Tetrahedron Lett. 59 (2018) 1343–1347.

[314] H. Weibarth, F. Mühlhaus, A. Gansauer, Synthesis 52 (2020) 2940–2947.

[315] A. Lidskog, Y. Li, K. Wärnmark, Catalysis 10 (2020) 705.

[316] E. Bednářová, Š. Malatinec, M. Kotora, Molecules 25 (2020) 958.

[317] Š. Malatinec, E. Bednářová, H. Tanaka, M. Kotora, Eur. J. Org Chem. (2021) 1249–1257.

[318] L. Yao, Q. Zhu, L. Wei, Z.-F. Wang, C.-J. Wang, Angew. Chem. Int. Ed. 55 (2016) 5829–5833.

[319] F. Broghammer, D. Brodbeck, T. Junge, R. Peters, Chem. Commun. 53 (2017) 1156–1159.

[320] K.-Y. Ye, T. McCallum, S. Lin, J. Am. Chem. Soc. 141 (2019) 9548–9554.

[321] S. Menino, A. Lattanzi, Chem. Eur J. 22 (2016) 3632–3642.

[322] M.R. Monaco, G. Pupo, B. List, Synlett 27 (2016) 1027–1040.

[323] W. Liu, X. Yang, Asian J. Org. Chem. 10 (2021) 692–710.

[324] C.D. Gheewala, B.E. Collins, T.H. Lambert, Science 351 (2016) 961–965.

[325] C. Yuan, J. Li, P. Li, ACS Omega 3 (2018) 6820–6826.

[326] R.E. Shelton, S. Sezer, D.M. Hodgson, Tetrahedron 76 (2020) 131701.

[327] Z. Sun, R. Lonsdale, X.-D. Kong, J.H. Xu, J. Zhou, M.T. Reetz, Angew. Chem. Int. Ed. 54 (2015) 12410–12415.

[328] Z. Sun, P. Lonsdale, L. Wu, G. Li, A. Li, J. Wang, J. Zhou, M.T. Reetz, ACS Catal. 6 (2016) 1590–1597.

[329] G. Li, H. Zhang, Z. Sun, X. Liu, M.T. Reetz, ACS Catal. 6 (2016) 3679–3687.

[330] Z. Sun, L. Wu, M. Bocola, H.C.S. Chan, R. Lonsdale, X.-D. Kong, S. Yuan, J. Zhou, M.T. Reetz, J. Am. Chem. Soc. 140 (2018) 310–318.

[331] A. Sandvoβ, J.M. Wiest, Chem. Eur J. 27 (2021) 5871–5877.

[332] Z. Wang, W.-X. Hong, J. Sun, Curr. Org. Chem. 20 (2016) 1851–1862.

[333] D. Li, D. Yang, L. Wang, X. Liu, X. Jiang, R. Wang, Chem. Eur J. 22 (2016) 17141–17144.

[334] L. Wang, D. Li, D. Yang, K. Wang, J. Wang, P. Wang, W. Su, R. Wang, Chem. Asian J. 11 (2016) 691–695.

[335] D. Li, Y. Wang, L. Wang, J. Wang, P. Wang, K. Wang, L. Lin, D. Liu, X. Jiang, D. Yang, Chem. Commun. 52 (2016) 9640–9643.

[336] L. Wang, D. Yang, D. Li, H. Zhu, P. Wang, X. Liu, L. Bai, R. Wang, Adv. Synth. Catal. 360 (2018) 4491–4496.

[337] D. Li, L. Wang, H. Zhu, L. Bai, Y. Yang, M. Zhang, D. Yang, R. Wang, Org. Lett. 21 (2019) 4717–4720.

[338] D. Li, K. Wang, L. Wang, Y. Wang, P. Wang, X. Liu, D. Yang, R. Wang, Org. Lett. 19 (2017) 3211–3214.

[339] J. Casas, C. Nájera, J.M. Sansano, J.M. Saá, Org. Lett. 4 (2002) 2589–2592.

[340] X. Li, J. Guo, L. Lin, H. Hu, F. Chang, X. Liu, X. Feng, Adv. Synth. Catal. 359 (2017) 3532–3537.

[341] X. Li, Q. Xiong, M. Guan, S. Dong, X. Liu, X. Feng, Org. Lett. 21 (2019) 6096–6101.

[342] Z. Chai, P.-J. Yang, H. Zhang, S. Wang, G. Yang, Angew. Chem. Int. Ed. 56 (2017) 650–654.

[343] N. Shiomi, M. Kurada, S. Nakamura, Chem. Commun. 53 (2017) 1817–1820.

[344] N. Shiomi, K. Yamamoto, K. Nagasaki, T. Hatanaka, Y. Funahashi, S. Nakamura, Org. Lett. 19 (2017) 74–77.

[345] M. Punk, C. Merkley, K. Kennedy, J.B. Morgan, ACS Catal. 6 (2016) 4694–4698.

[346] J. Zhang, W. Xiao, H. Hu, L. Lin, X. Liu, X. Feng, Chem. Eur J. 24 (2018) 13428–13431.

[347] Y. Zheng, Y. Huang, P. Gao, H. Liu, S. Murakami, R. Matsubara, M. Hayashi, Org. Lett. 23 (2021) 2411–2414.

[348] D. Qian, M. Chen, A.C. Bissember, J. Sun, Angew. Chem. Int. Ed. 57 (2018) 3763–3766.

[349] Z. Wang, F.K. Sheong, H.H.Y. Sung, I.D. Williams, Z. Lin, J. Sun, J. Am. Chem. Soc. 137 (2015) 5895–5898.

[350] M. Lautens, K. Fagnou, S. Hiebert, Acc. Chem. Res. 30 (2003) 48–58.

[351] C.C.J. Loh, M. Schmid, B. Peters, Y. Fang, M. Lautens, Angew. Chem. Int. Ed. 55 (2016) 4600–4604.

[352] S. Li, Z. Lu, L. Meng, J. Wang, Org. Lett. 18 (2016) 5276–5279.

[353] A. Sadeer, Y.J. Ong, T. Kojima, C.Q. Foo, Y. Li, S.A. Pullarkat, P.-H. Leung, Chem. Asian J. 13 (2018) 2829–2833.

[354] I.P. Beletskaya, C. Nájera, M. Yus, Chem. Soc. Rev. 49 (2020) 7101–7166.

[355] J. Yang, Y. Sekiguchi, N. Yoshikai, ACS Catal. 9 (2019) 5638–5644.

[356] Y. Li, J. Chen, Z. He, H. Qin, Y. Zhou, R. Khan, B. Fang, Org. Chem. Front. 4 (2017) 1921–1924.

[357] X. Xu, J. Chen, Z. He, Y. Zhou, B. Fan, Org. Biomol. Chem. 14 (2016) 2480–2486.

[358] X. He, J. Chen, X. Xu, F. Yang, C. Gu, Y. Zhou, B. Fan, Tetrahedron: Asymmetry (2017) 62–68.

[359] F. Fang, J. Chen, J. Xu, F. Ma, Y. Zhou, M.V. Shinde, B. Fan, Org. Lett. 18 (2016) 4832–4835.

[360] Y. Zhou, C. Gu, J. Chen, M. Zhu, F. Yang, J. Xu, B. Fan, Adv. Synth. Catal. 358 (2016) 3167–3172.

[361] W. Zhang, J. Chen, G. Zeng, F. Fang, J. Xu, W. Sun, M.V. Shinde, B. Fan, J. Org. Chem. 82 (2017) 2641–2649.

[362] M. Zhu, J. Chen, X. He, C. Gu, J. Xu, B. Fan, J. Org. Chem. 82 (2017) 3167–3173.

[363] Y.-h. Cho, V. Zunic, H. Senboku, M. Olsen, M. Lautens, J. Am. Chem. Soc. 128 (2006) 6837–6846.

[364] W. Yang, G. Cheng, Y. Li, X. Zhuo, D. Yang, Synthesis 49 (2017) 2025–2035.

[365] J. Chen, L. Zou, C. Zeng, Y. Zhou, B. Fang, Org. Lett. 20 (2018) 1283–1286.

[366] Y. Zhou, L. Yu, J. Chen, J. Xu, Z. He, G. Shen, B. Fan, Org. Lett. 20 (2018) 1291–1294.

[367] X. Fang, G. Zheng, X. Li, Angew. Chem. Int. Ed. 58 (2019) 322–326.

[368] P. Preethalayam, E. Jijy, P. Prakash, S.C. Sarngadharan, A. Vijayan, K.V. Radhakrishnan, J. John, Eur. J. Org Chem. (2020) 6588–6613.

Biography

Carmen Nájera was born in Nájera (La Rioja) in 1951 and graduated from the University of Zaragoza in 1973, obtaining her doctorate degree in chemistry from the University of Oviedo in 1979. She had postdoctoral stays at the ETH (Zurich), the Dyson Perrins Laboratory (Oxford), Harvard University, and Uppsala University. She became an associate professor in 1985 at the University of Oviedo and a full professor in 1993 at the University of Alicante. She is a coauthor of more than 400 papers (h 72), 6 patents and 30 book chapters and has supervised more than 50 PhD students. She is also on the editorial board of several international journals. She has been awarded the 2006 Organic Chemistry Prize by the Spanish Royal Society of Chemistry, the 2006 Rosalind Franklin International Lectureship by the English Royal Society, the SCF 2010 French-Spanish Prize by the Société Chimique de France, the IUPAC 2015 Distinguished Women in Chemistry or Chemical Engineering Award, the 2018 Serratosa lectureship and the Premio Julio Peláez 2021 to pioneering women in science. In 2012 she was named a full member of the Royal Spanish Academy of Sciences and was appointed as an active member of the European Academy of Sciences and Arts. Professor Nájera has been on the advisory board of several international journal and in 2016–2017 was named a ChemPubSoc Europe Fellow.

Francisco Foubelo was born in 1961. He studied chemistry at the University of Oviedo where he received B.S. (1984), M.S. (1986), and Ph.D. (1989) degrees. After a postdoctoral stay (1989–1991) as a Fulbright fellow at Princeton University, he moved to the University of Alicante where he became an associate professor in 1995 and a full professor in 2002. Dr Foubelo has co-authored more than 150 papers, and his current research interests are focused on the development of new synthetic methodologies involving chiral sulfinimines and on metal-promoted functionalization of alkenes and alkynes.

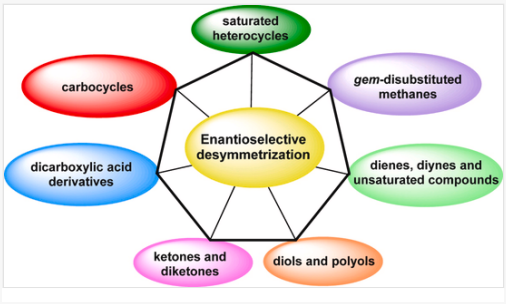
José Miguel Sansano was born in Rojales (Alicante) in 1965, and studied chemistry at the University of Alicante, where he obtained his B.Sc. and Ph.D. degrees in 1988 and 1994, respectively. His thesis was supervised by Prof. C. Nájera and focused on sulfone chemistry. After a two years postdoctoral stay at the University of Leeds (U.K.) with Prof. R. Grigg, he joined the University of Alicante in 1996, where he was appointed as an associate professor in 2001. In 2010 he was promoted as a full professor in the same university. He was invited as a visiting professor to Chuo University in 2014 and the UFRJ (Brazil). He is a coauthor of more than 150 articles (h 37) and has supervised 16 PhD students.

Miguel Yus was born in Zaragoza (Spain) in 1947, and received his BSc (1969), MSc (1971) and PhD (1973) degrees from the University of Zaragoza. After spending two years as a postdoctoral fellow at the Max Planck Institut für Kohlenforschung in Mülheim a. d. Ruhr he returned to Spain to the University of Oviedo where he became an associate professor in 1977 and was promoted to full professor in 1987 at the same university. In 1988 he moved to a chair in organic chemistry at the University of Alicante. Professor Yus has been a visiting professor at different institutions and universities including ETH-Zentrum, Oxford, Harvard, Uppsala, Marseille, Tucson, Okayama, Paris, Strasbourg, Bolonia, Sassari, Tokyo and Kyoto. He is a co-author of 650 papers (and six patents) and has supervised 63 doctoral students (theses already presented). He has delivered about 250 lectures, most of them abroad. His bibliometric data include more than 30,000 citations and an h-index of 78. He has received several international awards and has also been named an active academician by the European Academy of Sciences and Arts, and an academic member of the Athens Institute for Education and Research. Professor Yus has been on the advisory board of more than 30 international journals and is also the editor-in-chief of Letters in Organic Chemistry and Open Chemistry. Professor Yus founded a new chemical company MEDALCHEMY S.L. to commercialize fine chemicals.

Graphical abstract

Images are optimised for fast web viewing. Click on the image to view the original version.

alt-text: Image 1



Queries and Answers

Q1

Query: Please confirm that the provided **email** "cnajera@ua.es" is the correct address for official communication, else provide an alternate e-mail address to replace the existing one, because private e-mail addresses should not be used in articles as the address for communication.

Answer:

Q2

Query: Have we correctly interpreted the following funding source(s) and country names you cited in your article: University of Alicante, Spain; FEDER, Spain; Generalitat Valenciana, Spain; MINECO, Spain; Ministerio de Ciencia, Innovación y Universidades, Spain?

Answer:

Q3

Query: The **Uncited References** section comprises references that occur in the reference list but are not available in the body of the article text. Please cite each reference in the text or, alternatively, delete it. Any reference not dealt with will be retained in this section.

Answer:

Q4

Query: Please confirm that **given names and surnames** have been identified correctly and are presented in the desired order and please carefully verify the spelling of all authors' names.

Answer:

Q5

Query: Your article is registered as a regular item and is being processed for inclusion in a regular issue of the journal. If this is NOT correct and your article belongs to a Special Issue/Collection please contact a.baker.2@elsevier.com immediately prior to returning your corrections.

Answer: