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Review

Recent Advances in Selected Asymmetric Reactions Promoted by Chiral Catalysts: Cyclopropanations, Friedel–Crafts, Mannich, Michael and Other Zinc-Mediated Processes—An Update

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Abstract: The main purpose of this review article is to present selected asymmetric synthesis reactions in which chemical and stereochemical outcomes are dependent on the use of an appropriate chiral catalyst. Optically pure or enantiomerically enriched products of such transformations may find further applications in various fields. Among an extremely wide variety of asymmetric reactions catalyzed by chiral systems, we are interested in: asymmetric cyclopropanation, Friedel–Crafts reaction, Mannich and Michael reaction, and other stereoselective processes conducted in the presence of zinc ions. This paper describes the achievements of the above-mentioned asymmetric transformations in the last three years. The choice of reactions is related to the research that has been carried out in our laboratory for many years.

Keywords: asymmetric synthesis; chiral catalyst; cyclopropanation; Mannich reaction; Michael reaction; stereoselectivity; zinc ions

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1. Introduction

The synthesis of optically pure or enantiomerically enriched compounds has become one of the most important areas of interest in recent decades in modern synthetic organic chemistry [1]. Substances of high optical purity are still used in many industrial sectors, including the pharmaceutical and food industries. Chemists working in both academia and industry must agree with the fact that single chirality plays a huge role in nature and that biological properties are closely related to the absolute configuration of the product [2]. The opposite enantiomers act differently on living organisms and may exhibit different activities. Some of the differences are huge, ranging from different tastes and smells to even teratogenic (fetal-damaging) effects [3]. Between 1958 and 1962, thalidomide-racemic sedative drug, taken by pregnant women, damaged more than 10,000 fetuses worldwide [4]. This drastic example seems to be sufficient proof that the synthesis of optically pure substances used especially in the pharmaceutical and food industries is still gaining more and more importance.

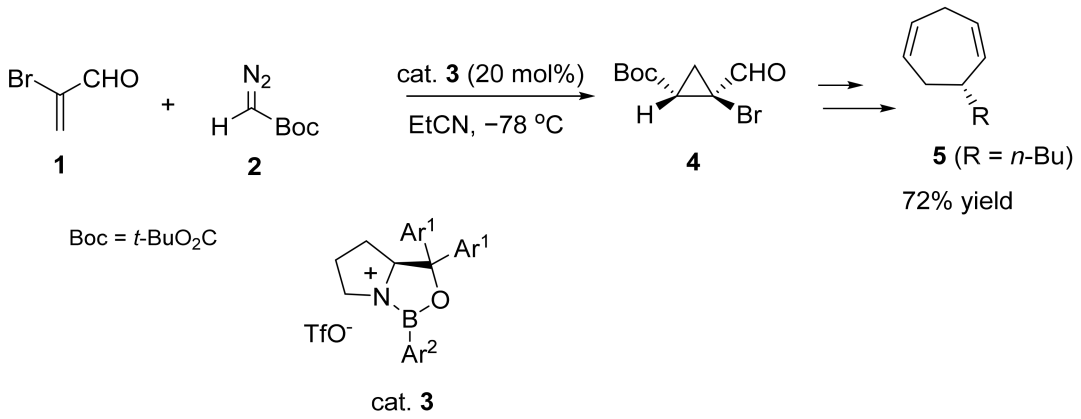
There are three main strategies for the synthesis of enantiomerically pure substances: the first one is a methodology based on the use of naturally occurring substances with defined absolute configuration, the second resolution of racemic mixtures (kinetic resolution and deracemization techniques) [5], and finally, asymmetric synthesis in which one or more chiral centers are generated in the substrate. The subject of this review article is closely related to the last methodology, i.e., asymmetric synthesis. There are several approaches used in asymmetric synthesis; however, we focused on the use of chiral catalysts. The large number of asymmetric reactions studied and the dynamically developing synthesis of new chiral catalysts made the preparation of this review article quite difficult. However, we have used the knowledge derived from the research conducted in our laboratory. Thanks to our

previous experience with asymmetric cyclopropanation reactions [6], Friedel–Crafts alkylation [7], Mannich [8,9] and Michael [10] reactions, and other asymmetric transformations performed in the presence of zinc ions [11], we decided to describe recent achievements in the field of these asymmetric transformations.

2. Asymmetric Cyclopropanation Reactions

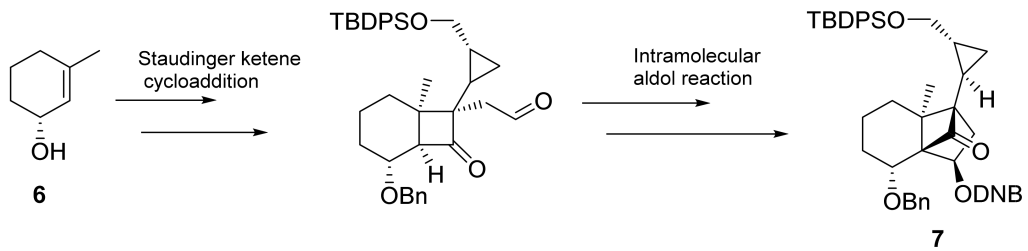
Asymmetric cyclopropanation is currently one of the most used methods for creating new C-C bonds, as a cyclopropane ring having a unique steric and electronic properties is a structural motif present in many biologically active molecules, e.g., Cabozantinib, Simeprevir, Lumacaftor, etc. [12]. Some synthetic approaches with or without transition metals to achieve cyclopropyl ring have been reviewed in 2018 [13]. Moreover, some examples illustrating relationships between pharmacological activity and structure of various cyclopropyl derivatives have also been reported in 2018 [14].

Dictyopterenes are chemical compounds occurring in marine and freshwater environments and being sexual attractants or pheromones [15]. The asymmetric synthesis of Dictyopterene C′ **5** and its derivatives was performed using asymmetric cyclopropanation as one of the steps. α,β-Unsaturated aldehydes **1** and α-substituted α-diazoesters **2** took part in the reaction promoted by a chiral oxazaborolidinium ion catalyst (COBI) **3** (Scheme 1) [16]. Further transformations of cyclopropyl derivatives of type **4** including Julia–Kocienski reaction and Sonogashira and Suzuki coupling led to the corresponding dictyopterenes **5** [16].



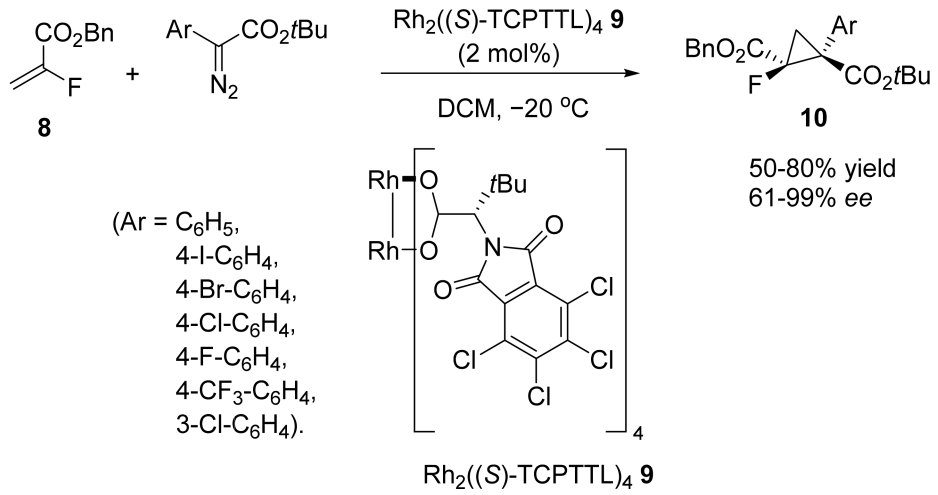
Scheme 1. Asymmetric synthesis of Dictyopterene C′.

Asymmetric Simmons–Smith cyclopropanation using diiodomethane and diethylzinc was applied in multi-step synthesis of the core of solanoeclepin A **7** (Scheme 2) which is a hatching agent of potato cyst nematodes [17]. Tricyclo [5.2.1.0] decane skeleton of solanoeclepin A was constructed starting from (*R*)-seudenol **6** (Scheme 2) [17].



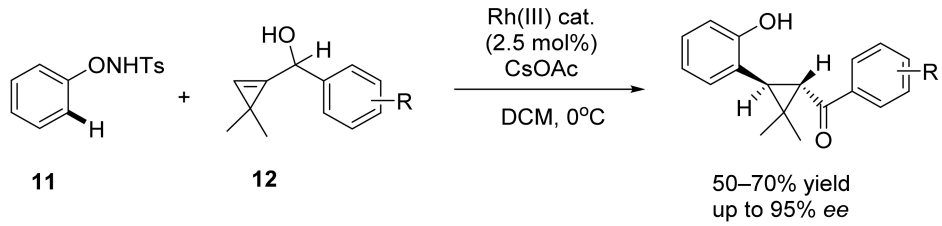
Scheme 2. Synthesis of solanoeclepin A core starting from (*R*)-seudenol.

Two further literature reports on the asymmetric cyclopropanation reaction include both experimental and theoretical studies [18,19]. In the first one, α-fluoroacrylates **8** were subjected to enantioselective cyclopropanation promoted by chiral rhodium catalysts **9** (Scheme 3) [18]. The corresponding cyclopropyl junctions **10** were formed with excellent enantio- and diastereoselectivities [18]. Monofluorinated cyclopropane derivatives have inter alia, antiviral (anti-herpetic) and antibacterial properties; the presence of fluorine and cyclopropane increases the bioavailability, selectivity and similarity to the respective receptors.



Scheme 3. Enantioselective cyclopropanation of α-fluoroacrylates.

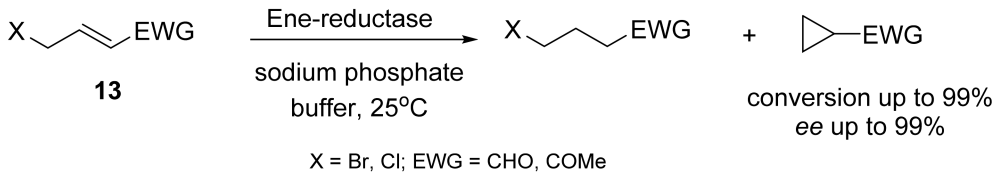
Chiral rhodium catalysts were also applied in stereoselective cyclopropanation of *N*-phenoxylsulfonamides **11** with cyclopropenyl secondary alcohols **12** (Scheme 4) [19]. A very wide spectrum of substrates was tested and, in most cases, the desired products were obtained in high chemical yields with excellent enantioselectivities and diastereoselectivity [19]. This type of cyclopropane moiety is the structural basis of drugs such as milnacipran and (+)-Tranylcypromine.



R = 4-Me, 3-Me, 2-Me, 4-^{i}Pr, 4-*t*-Bu, 4-OMe, 4-OPh, 4-OBn, 4-Ph, 4-Cl, 4-Br, 2-F, 3-F, 4-F, 4-CF_3, 4-OCF_3, 2-NO_2, 3-F and 3-Cl, 3,4-Me, 3,5-F and 2- and 3- furyl, 1- i 2-naphthyl.

Scheme 4. Stereoselective cyclopropanation of *N*-phenoxylsulfonamides.

An original and interesting approach to the cyclopropanation process was reported by Breinbauer et al. The enzymes ene reductases were used as catalysts in the reaction of reduction in carbon-carbon double bonds in α,β-unsaturated compounds **13** with electron-withdrawing group [20]. It turned out that this type of enzyme also catalyzes the process of creating carbon-carbon bonds; thus, the aforementioned α,β-unsaturated systems underwent reductive cyclization. This new enzymatic transformation allows access to chiral cyclopropyl derivatives with excellent *ee* (up to 99%) (Scheme 5) [20].

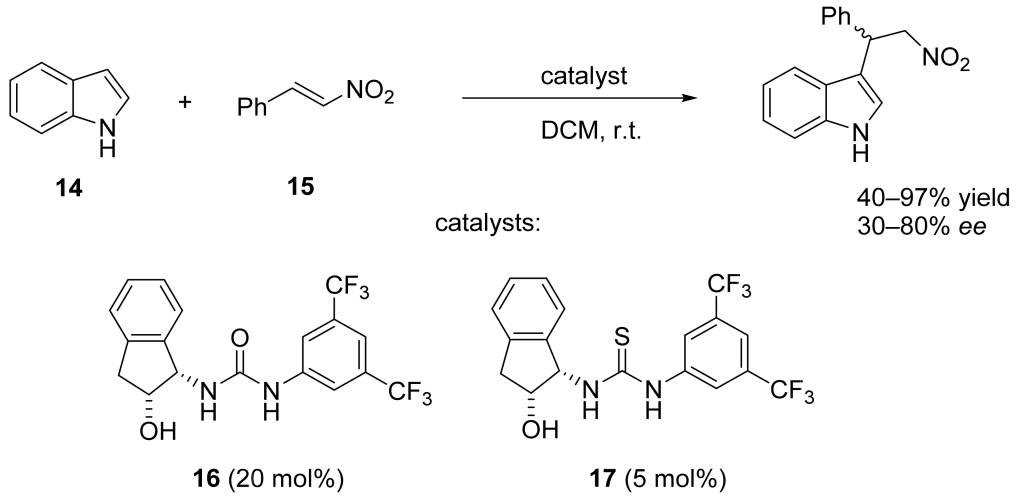


Scheme 5. Enzyme-promoted C-C bond formation via reductive cyclization.

3. Asymmetric Friedel–Crafts Reactions

Asymmetric Friedel–Crafts reaction is another widely used method for the enantioselective construction of carbon-carbon bonds [21]. The title transformation is often used in the synthesis of biologically active compounds [22] and some organocatalytic approaches have been compiled in a review article in 2019 [23]. Among the extremely wide variety of chiral sources used in asymmetric Friedel–Crafts reaction, in this review, special attention is paid to systems such as chiral derivatives of urea [24], thiourea [24], squaramide, chiral phosphoric acids and various complexes of N-heterocycles with metals.

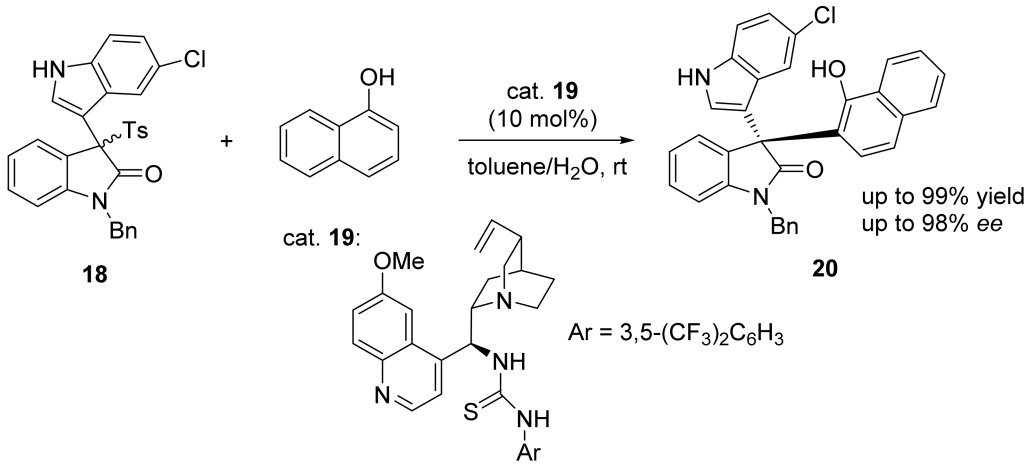
Herrera et al. studied the activation of urea- and thiourea-derived catalysts in an asymmetric Friedel–Crafts reaction of indole **14** and nitrostyrene **15** as model substrates (Scheme 6) [25,26].



Scheme 6. Reaction of indole and nitrostyrene promoted by urea or thiourea catalysts.

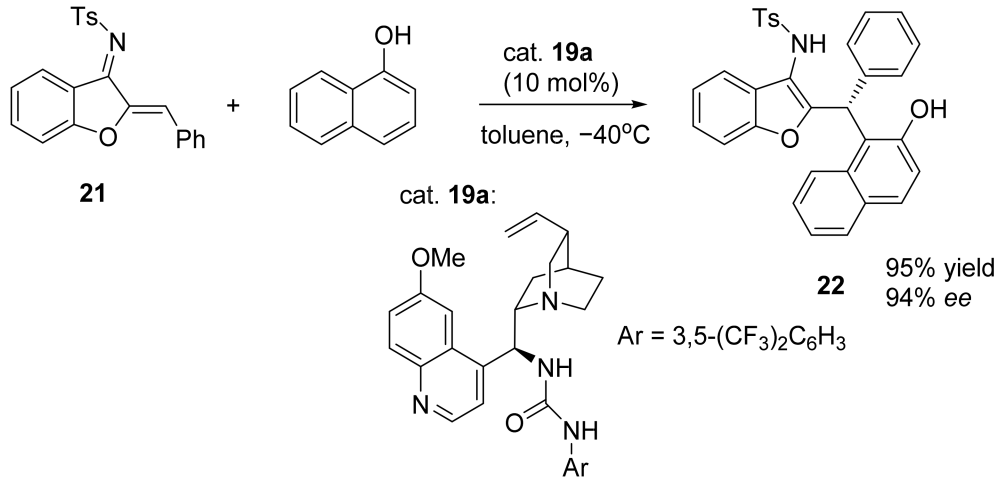
In the first contribution authors showed that the addition of an external Brönsted acid (*rac*-mandelic acid) enhanced the catalytic activity of the urea **16** system, increasing the enantioselectivity to 68% *ee* [25]. In the second study, chiral thiourea derivatives were activated with metals, leading to the best results in terms of enantioselectivity for the gold (I) complex of thiourea **17** [26].

An asymmetric alkylation of sulfonylindoles of type **18** with naphthol and its derivatives was performed by Han and co-workers using bifunctional catalysts bearing urea or a thiourea motif [27]. The corresponding products of type **20** were formed in the highest yields and enantiomeric excesses using thiourea **19** (Scheme 7). Additionally, among many solvents tested, the authors showed that the two-phase water–toluene system is the best one [27]. Taking into account the structure of compound **18**, the proposed method may be useful in the synthesis of such natural compounds as (+)-gliocladin C, (+)-bionectin A or leptosin D.



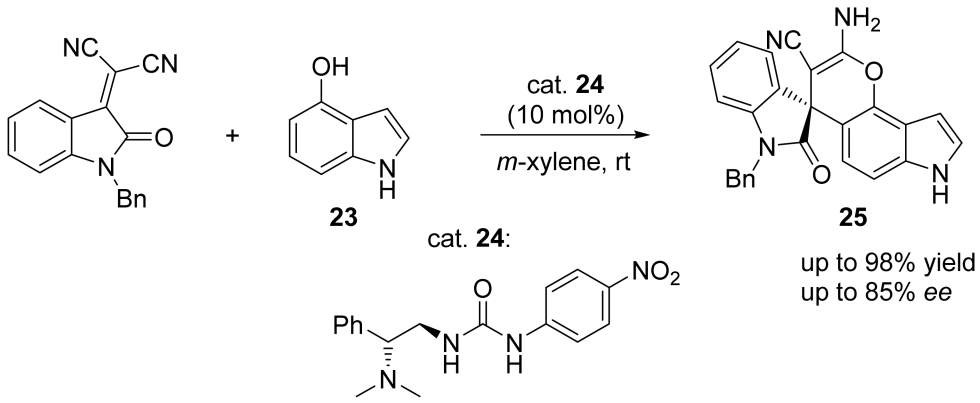
Scheme 7. Reaction of sulfonylindole with naphthol catalyzed by thiourea **19**.

A similar Friedel–Crafts transformation consisting in arylation of 1-azadienes of type **21** was reported in 2020 [28]. The desired product **22** was obtained in very high chemical yield (95%), and with an excellent enantiomeric ratio (97:3), when the urea-analog of system **19** (**19a**) was applied as catalyst (Scheme 8) [28]. The same reaction was investigated using thiourea bifunctional catalyst **19** which led to the appropriate chiral product with a moderate yield (72%) and enantioselectivity (62% of *ee*) [29]. It should be stressed that chiral triarylmethanes are the structural skeleton of many systems that exhibit antiviral and antibacterial effects, as well as a drug for tuberculosis or skin diseases.



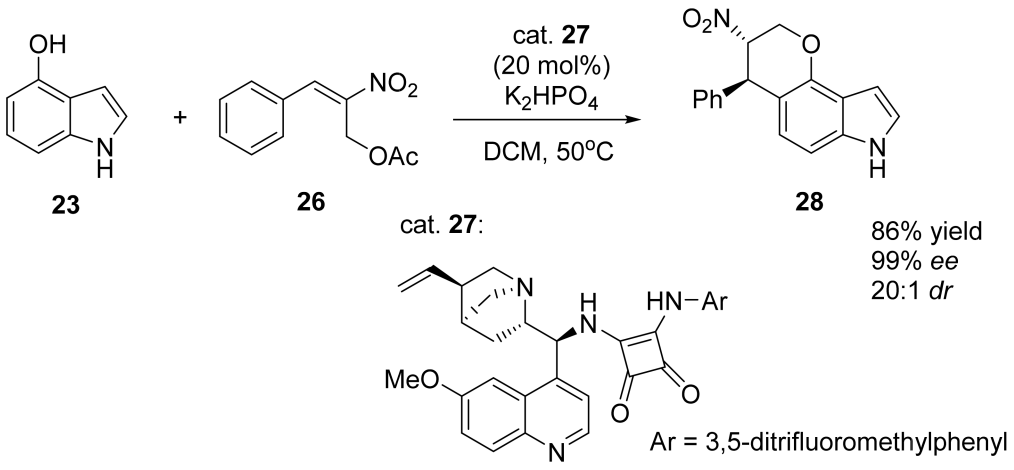
Scheme 8. Urea-promoted arylation of 1-azadienes.

Friedel–Crafts alkylation/cyclization of 4-hydroxyindole **23** promoted by bifunctional tertiary amine-urea catalyst **24** was reported by Lin and Duan et al. [30]. The corresponding spirooxindole-pyranoindole products of type **25** were formed very efficiently in terms of yield and enantioselectivity (Scheme 9) [30]. Indole derivatives are found in many drugs, while systems structurally similar to compound **25** have predominantly anti-malarial activity (e.g., NID609).



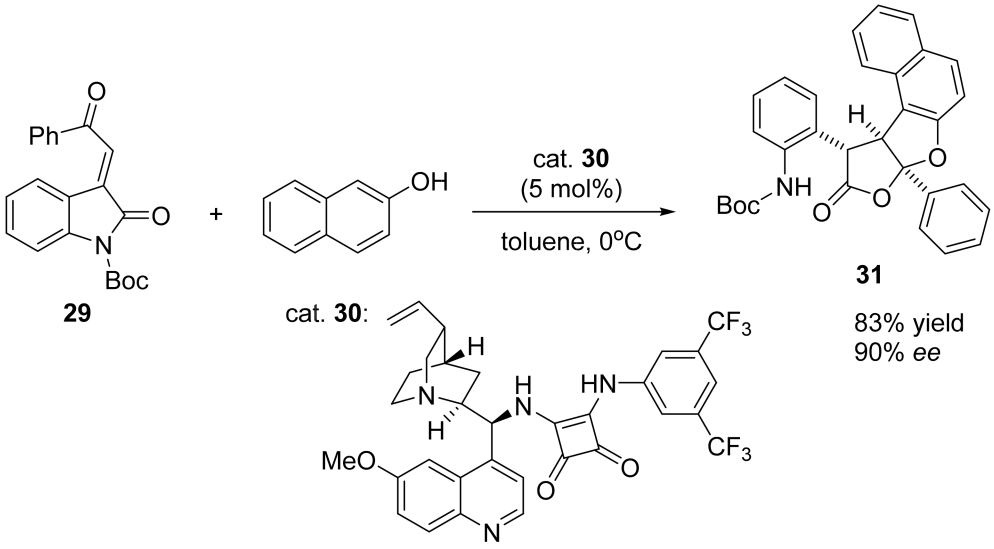
Scheme 9. Alkylation/cyclization of 4-hydroxyindole in the presence of urea system **24**.

Friedel–Crafts functionalization of 4-hydroxyindole **23** with (*E*)-2-nitroallylic acetate **26** was successfully carried out using bifunctional squaramide catalyst **27** (Scheme 10) [31]. Chiral product **28** was formed in 86% yield, with over 99% of *ee* and diastereomeric ratio over 20:1 when system **27** was applied in DCM at 50 °C in the presence of dipotassium hydrogen phosphate and 4 Å molecular sieves [31]. It should be mentioned that thiourea catalysts showed weaker catalytic activity in this process [31]. As with other indole systems, it is present in many drugs and natural compounds.



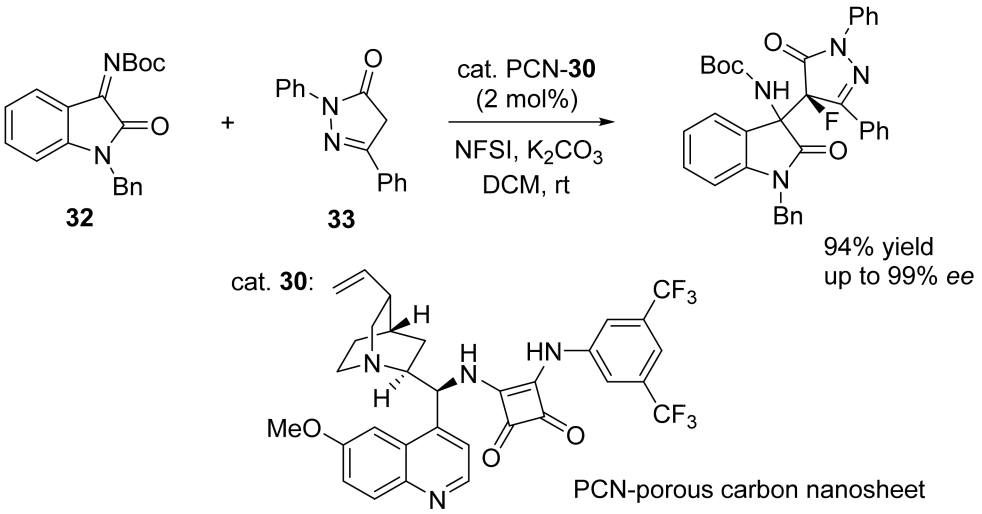
Scheme 10. Friedel–Crafts reaction of indole catalyzed by squaramide derivative **27**.

Furo [2,3-*b*] benzofuranones were synthesized via efficient asymmetric Friedel–Crafts alkylation/hemiketalization/lactonization cascade reaction [32]. The search for new methods of the synthesis of chiral furo [2,3-*b*] benzofuranones is desirable due to the high biological (e.g., antibacterial, anti-thrombotic) activity of such systems. In the model reaction, 3-ylidene oxindole **29** was treated by 2-naphthol. The corresponding product **31** was obtained in the highest yield (83%) and enantioselectivity (90% of *ee*) in toluene when squaramide **30** was used as chiral promoter (Scheme 11). Thiourea derivatives were also tested but the results were not as significant as for squaramide [32].



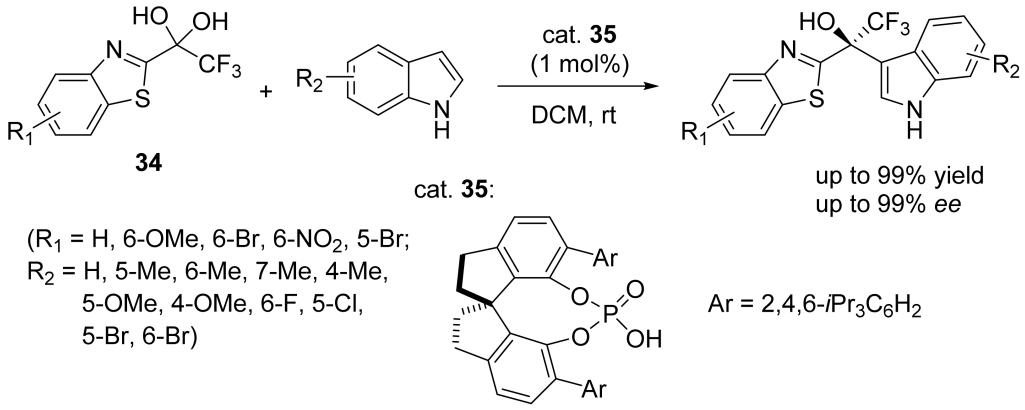
Scheme 11. Synthesis of furo [2,3-*b*] benzofuranones promoted by squaramide **30**.

Porous carbon nanosheet-supported squaramide **30** catalysts were successfully used for highly enantioselective Friedel–Crafts reaction between isatin ketimine **32** and pyrazolone **33** (Scheme 12) [33]. The best results in terms of yield (94%) and *ee* (up to 99%) were achieved after 15 min in DCM in the presence of potassium carbonate and *N*-fluorobenzenesulfonimide (NFSI) [33].



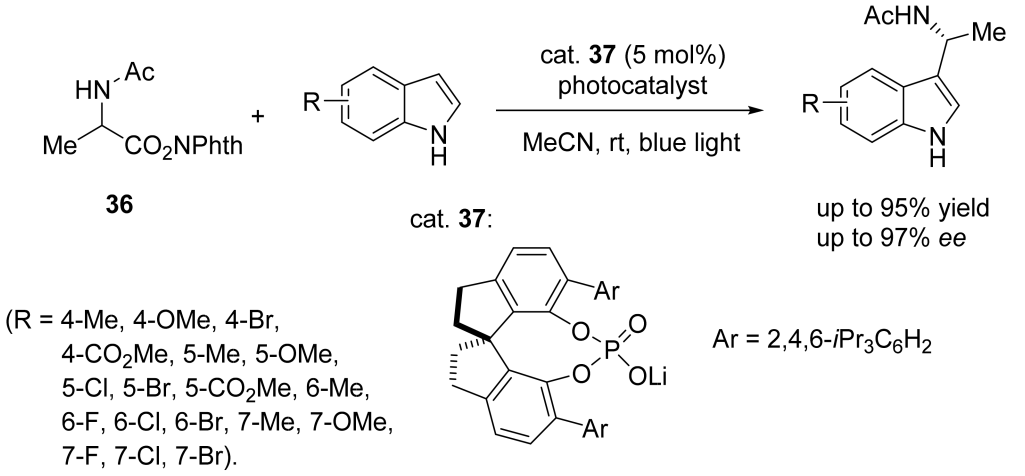
Scheme 12. Friedel–Crafts reaction of pyrazolone with isatine ketimine.

Chiral phosphoric acids acted as catalysts in asymmetric Friedel–Crafts alkylation of indoles with trifluoromethyl ketone hydrates **34** bearing a benzothiazole moiety (Scheme 13) [34]. The most successful transformation was achieved in case of the use of **35** as the chiral catalyst [34]. In this synthesis, special emphasis was placed on the chiral α-trifluoromethyl tertiary alcohol, which is present in many Anti-HIV drugs.



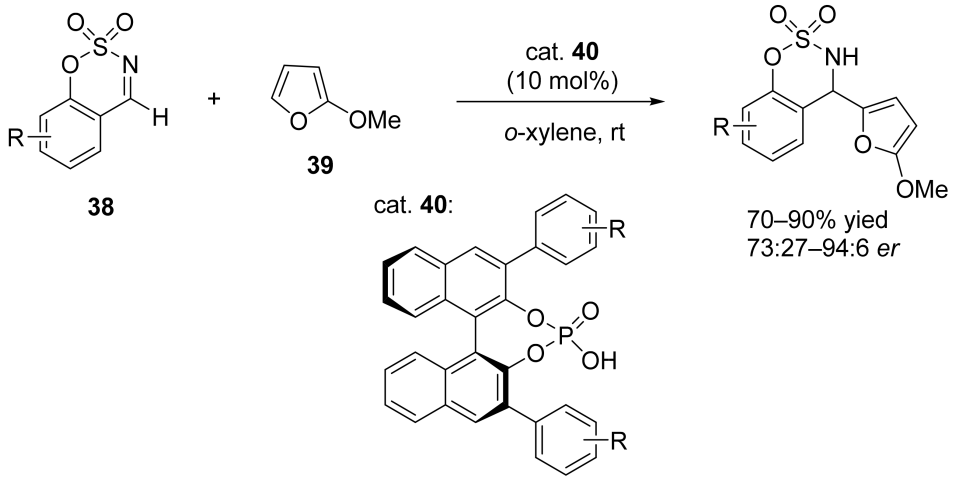
Scheme 13. Acid-catalyzed Friedel–Crafts alkylation of indoles.

Similar catalysts were examined in the asymmetric Friedel–Crafts reaction of indoles with in situ generated *N*-acyl imines from alanine-derived *N*-(acyloxy) phthalimide **36** (Scheme 14) [35]. Reactions were performed under blue LED light in the presence of ruthenium or iridium photocatalysts [35]. The most efficient model reaction (86% yield, 90% *ee*) was carried out in the presence lithium salt **37**.



Scheme 14. Friedel–Crafts reaction of indoles with in situ generated *N*-acyl imines.

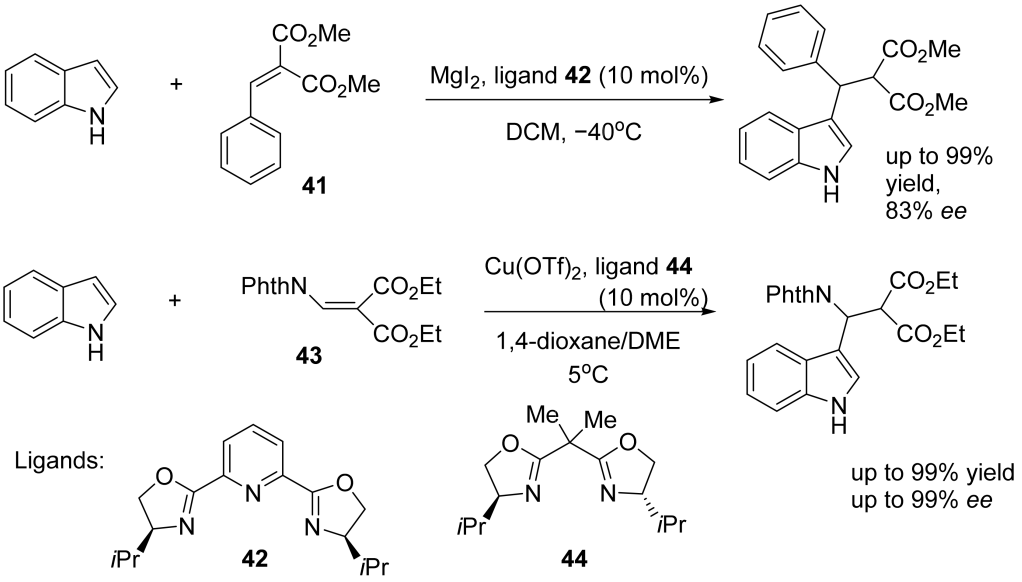
Enantioselective Friedel–Crafts reaction of cyclic *N*-sulfimines **38** with 2-methoxyfurane **39** catalyzed by chiral BINOL-derived phosphoric acids was described in 2019 (Scheme 15) [36]. The application of chiral derivative **40** in *o*-xylene at room temperature gave the best results in terms of chemical yield and enantiomeric ratio [36]. The asymmetric FC reaction in which furan is the substrate is less understood as compared to indole. The furan ring is present in many natural compounds: (-)-furodysinin, fraxinellone (can be used as a pesticide but is non-toxic to mammals) or lophotoxin (it is an antagonist of the nicotinic acetylcholine receptor).



Scheme 15. Enantioselective reaction of *N*-sulfimines **38** with 2-methoxyfurane.

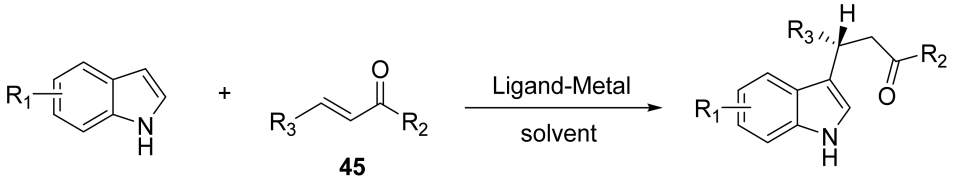
BINOL-derived chiral phosphoric acids are among the most widely used phosphorus derivatives to catalyze the asymmetric Friedel–Crafts reaction [37]. In addition to the reaction cited above, other selected examples of application of such catalysts are: alkylation of indoles with β-substituted cyclopenteneimines leading to β-indolyl cyclopentanones [38], asymmetric arylation of 2,2,2-trifluoroacetophenones [39], reaction of indoles with α-iminophosphonates [40], tandem three-component reaction of indole with aldehydes and *p*-toluenesulfonamide [41] and reaction of indoles with 3-indolylsulfamidates [42].

Beletskaya et al. described asymmetric Friedel–Crafts reactions of indoles with arylidene malonates **41** in the presence of magnesium iodide [43] and with phthaloyl-protected aminomethylenemalonate **43** in the presence of $Cu(OTf)_2$ [44]. The processes were catalyzed by PyBox [43] or *i*PrBox [44], respectively (Scheme 16).



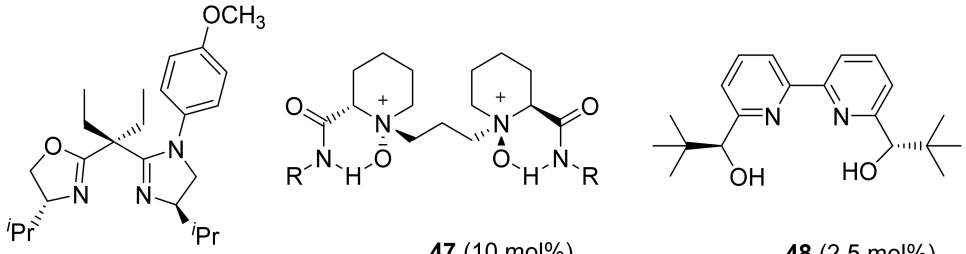
Scheme 16. Reactions of indole with malonate derivatives promoted by PyBox and *i*PrBox.

The asymmetric reaction of indoles with α,β-unsaturated carbonyl compounds **45** (enones) was carried out using three similar catalytic systems (Scheme 17) [45–47]. In the first contribution, reaction was promoted by imidazoline-oxazoline **46** complex with $Cu(OTf)_2$ (acetonitrile, room temperature), leading to indole derivatives acting as novel α-glucosidase inhibitors in vitro [45]. The second approach comprises a utilization of chiral *N*,*N*-dioxide **47**-scandium(III) complexes in dichloromethane at 35 °C [46], and finally, the third work relies on the application of cationic aqua complex of 2,2′-bypiridine **48** with palladium(II) in water at room temperature [47].



(R_1 = H, 5-Me, 6-Me, 5-OMe, 5-OBn, 5-F, 5-Cl, 5-Br; R_2 = Ph, Cy, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-CF_3-C_6H_4, 4-FC_6H_4, 4-ClC_6H_4, 4-$NO_2C_6H_4$, 2-thienyl, 2-furyl, 2-ferrocenyl; R_3 = Me, CF_3, Et)

Ligands:



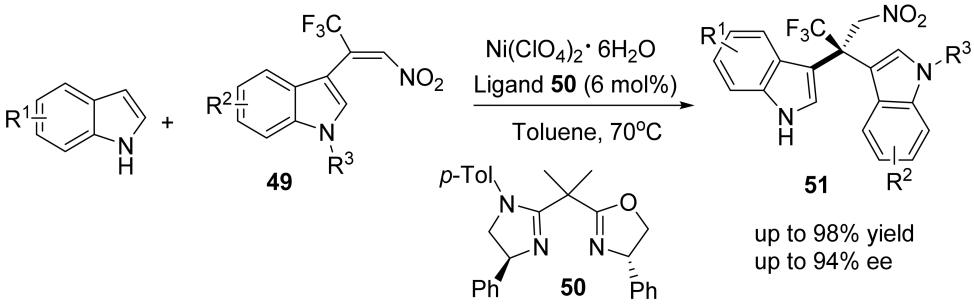
46 (10 mol%)
20–90% yield
89–98% *ee*

47 (10 mol%)
99% yield
85–92% *ee*

48 (2.5 mol%)
40–99% yield
78–92% *ee*

Scheme 17. Reaction of indole with enones.

Chiral bis (3-indolyl) methanes **51** were synthesized in high yields and in a highly enantioselective manner via asymmetric Friedel–Crafts alkylation of indoles with trifluoromethylated nitroalkenes **49** (Scheme 18) [48]. Reactions were promoted by a nickel(II) complex of imidazoline oxazoline **50**. Systems of type **51** have antibacterial and antifungal properties, inhibit the growth of cancer cells, and are also colorimetric sensors.

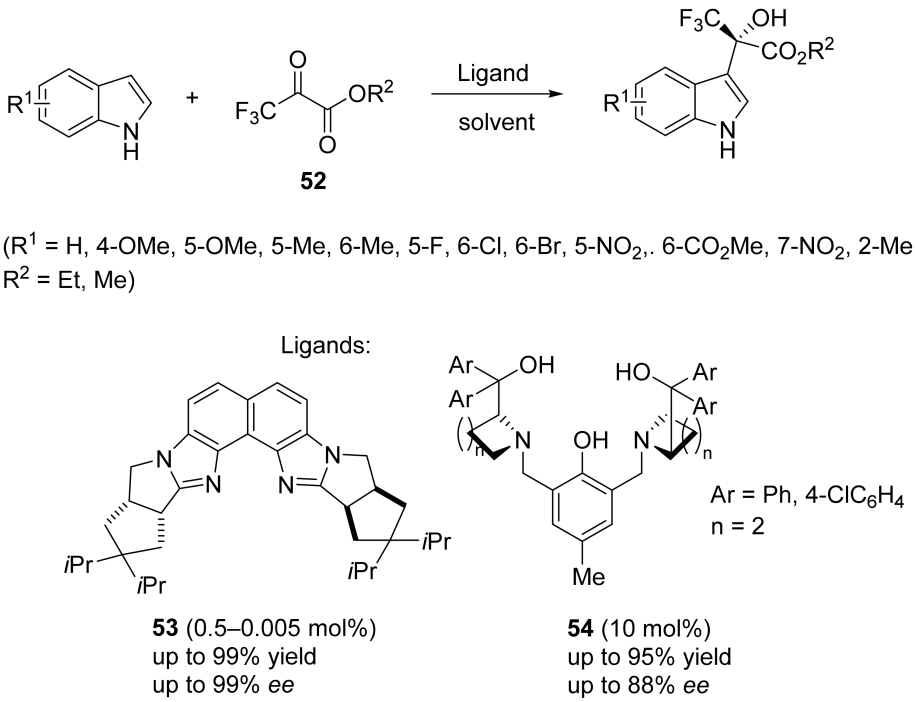


up to 98% yield
up to 94% ee

(R^1 = 5-F, 5-F, 5-Cl, 5-Br, 5-Me, 5-OMe, 6-Cl, 6-Me, 6-OMe, 7-Me, 7-OMe;
R^2 = 5-F, 5-Br, 5-Me, 5-OMe, 5-CO2Me, 6-Me, 7-Me, 7-OMe;
R^3 = Ts, Boc)

Scheme 18. Synthesis of chiral bis (3-indolyl) methanes.

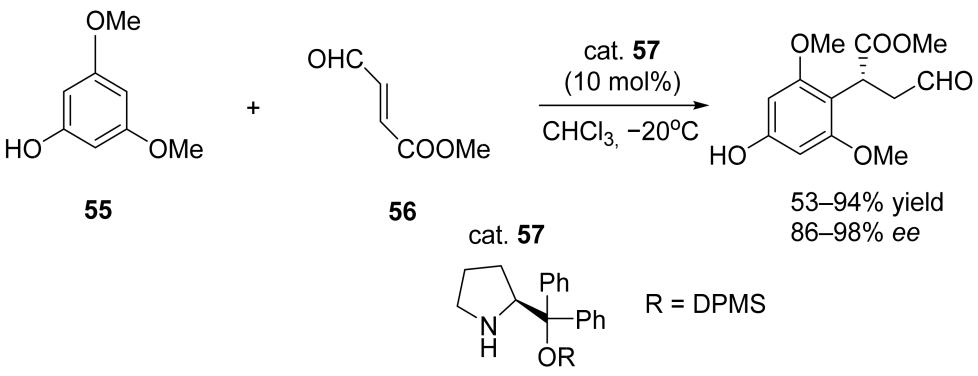
Asymmetric Friedel–Crafts reactions of indoles with trifluoromethyl pyruvate **52** were independently described in 2018 [49,50]. Kitamura et al. applied complexes of BOX-type **53** with $Cu(OTf)_2$ in cyclopentyl methyl ether (CPME) at 0 °C [49]. In turn, Wang and Yang et al. carried out this process using Trost's dinuclear zinc-ProPhenol catalyst **54** in dichloromethane at 10 °C in the presence of diethylzinc (Scheme 19) [50].



Scheme 19. Alkylation of indoles with trifluoromethyl pyruvates.

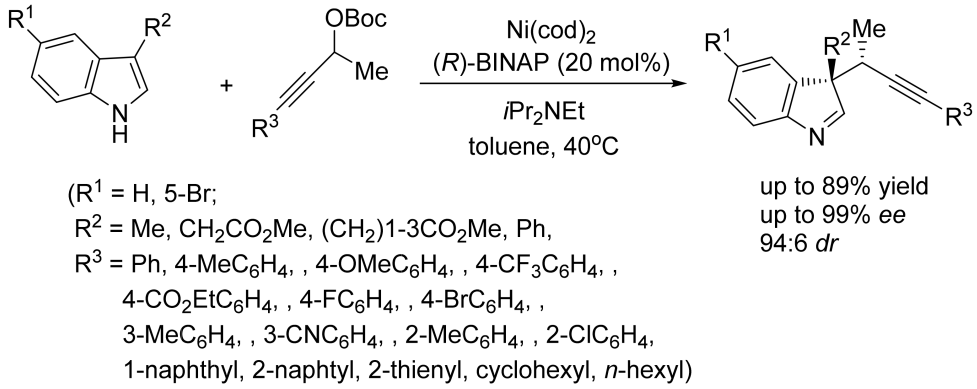
Similar dinuclear zinc catalytic systems were also used in the synthesis of 2,5-pyrrolidinyl dispirooxindoles [51] and tetrahydrofuran spirooxindoles [52] via cascade reactions, where one of the steps is a Friedel–Crafts process. Moreover, this type of chiral catalyst was successfully utilized for Friedel–Crafts reaction of pyrrole with chalcones [53].

The organocatalytic Friedel–Crafts alkylation of phloroglucinol derivatives **55** with enals **56** was described by Zu et al. [54]. The corresponding chiral products were afforded in high yields and enantioselectivities (Scheme 20) when diphenylprolinol TMS ether **57** was applied as the catalyst. This reaction opens up access to total synthesis of (+)-aflatoxin B_2 [54].



Scheme 20. Enantioselective alkylation of phloroglucinol derivatives.

The asymmetric propargylation of 3-substituted indoles via Friedel–Crafts process catalyzed by Ni(cod)$_2$ and (*R*)-BINAP afforded the corresponding products bearing internal alkyne group with excellent enantio- and diastereoselectivities (Scheme 21) [55].



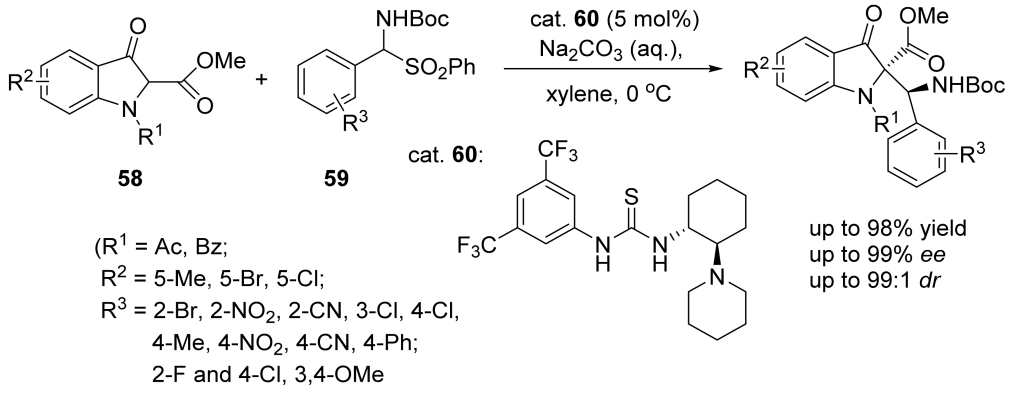
Scheme 21. Asymmetric Friedel–Crafts propargylation of indoles.

At the end of this chapter, it is worth mentioning a few more non-obvious approaches to the asymmetric Friedel–Crafts reaction. They are for sure the use of *N*-heterocyclic carbenes as catalysts in the synthesis of indole-fused polycyclic alcohols [56], guanosine-based self-assembly as catalytic system [57], and various DNA-employing catalytic systems [58–60].

4. Asymmetric Mannich Reactions

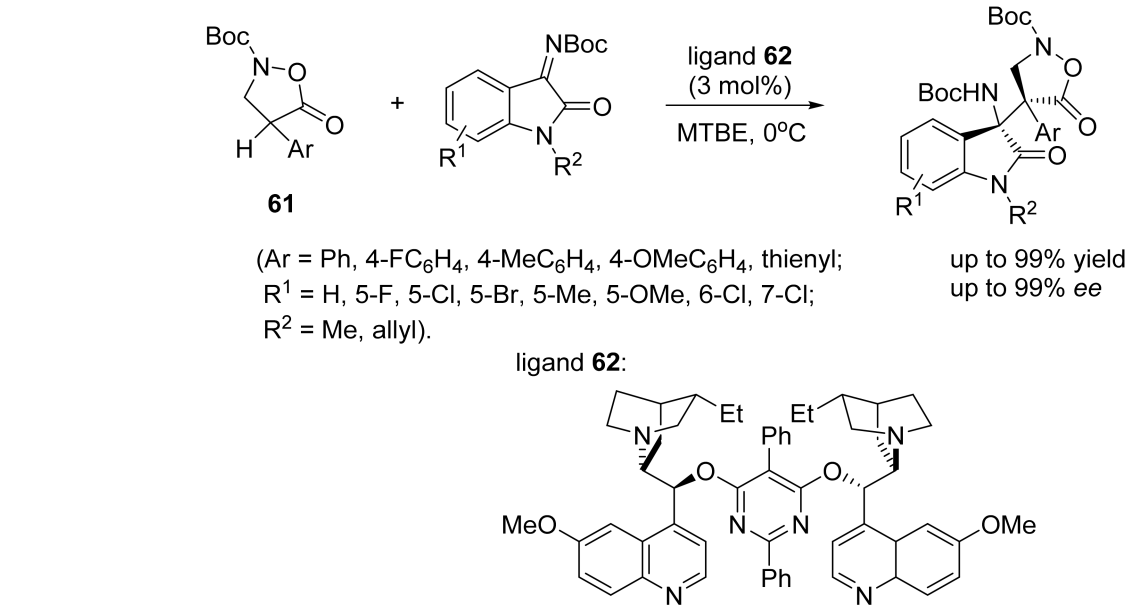
Asymmetric Mannich reaction is another process of enantioselective formation of carbon-carbon bonds, which can result in the formation of useful building blocks and compounds exhibiting biological activity.

Bifunctional thiourea systems were employed to the reaction between 3-indolinone-2-carboxylates **58** to *N*-Boc-benzaldimines generated in situ from α-amidosulfones **59** [61]. The best results in terms of chemical yield, enantio- and diastereoselectivity were obtained with the use of thiourea **60** (Scheme 22) [61]. Chiral derivatives of isatins occur in the nature; these are compounds such as (+)-isatisine A, trigonoliimine or mersicarpine. All three exhibit antiviral properties.



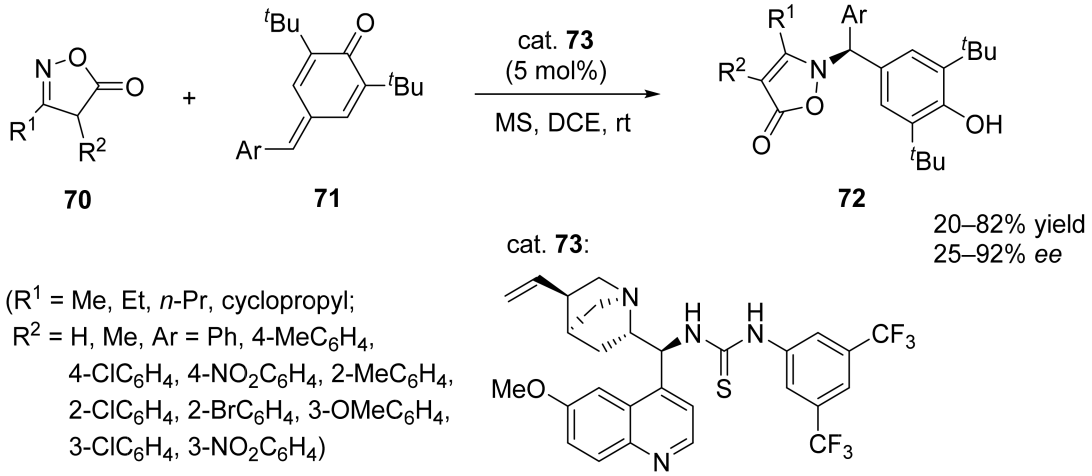
Scheme 22. Asymmetric Mannich reaction leading to chiral β-amino esters.

4-Substituted isoxazolidin-5-ones **61** were reacted with isatin-derived imines in the presence of (DHQD)$_2$PYR ligand **62** (Scheme 23) [62]. Reactions performed in methyl *tert*-butyl ether (MTBE) at 0 °C gave the corresponding Mannich products in almost quantitative yields, and excellent enantioselectivity (99%) and diastereoselectivity (20:1 of *d.r.*). The obtained products are building blocks for the synthesis of systems with bactericidal properties.



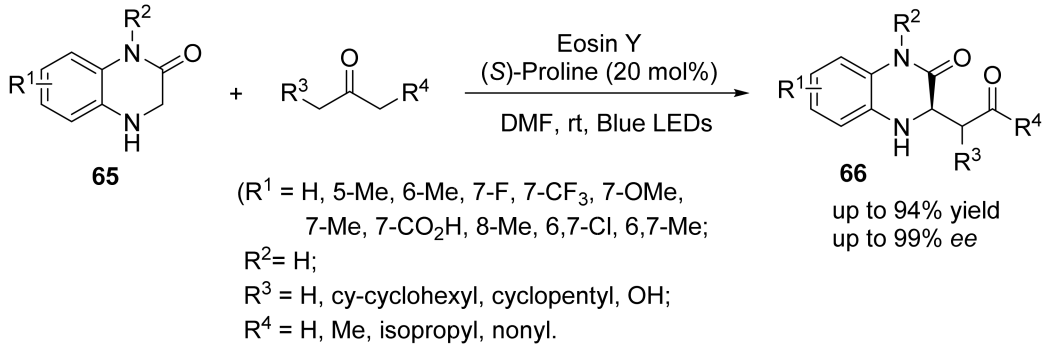
Scheme 23. Mannich reaction of isoxazolidin-5-ones with isatin-derived imines.

Catalytic asymmetric Mannich reaction of *N*-Boc-aldimines with α,β-unsaturated pyrazoleamides **63** was successfully catalyzed by the complex of copper(I)-(*R*)-DTBM-SEGPHOS **64** in the presence of triethylamine leading to the corresponding *syn*-vinylogous products in a highly enantioselective and diastereoselective manner (Scheme 24) [63].



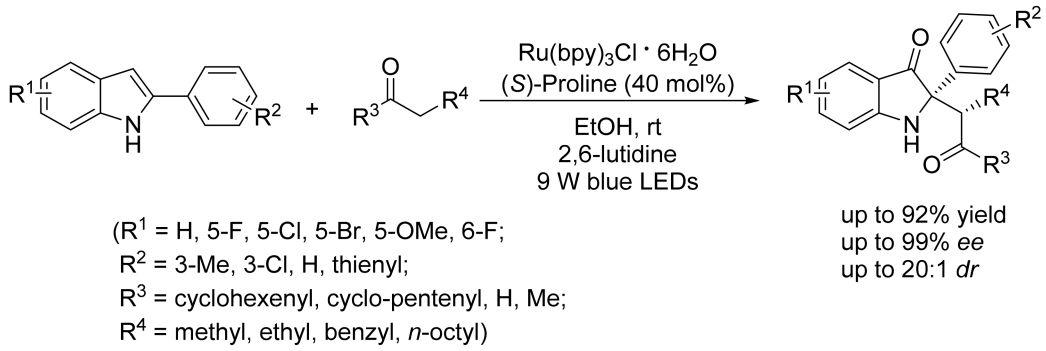
Scheme 24. Asymmetric Mannich reaction of *N*-Boc aldimines with pyrazoleamides.

One of the most common chiral catalysts used in the asymmetric Mannich reaction, namely L-proline, was combined with the corresponding photocatalysts and used in enantioselective Mannich reaction of dihydroquinoxalinones **65** with ketones [64] and in the synthesis of C2-quaternary indolin-3-ones [65]. The dihydroquinoxalinone skeleton is found in many natural and synthetic compounds, which are drugs and plant protection products. In the first work, chiral quinoxaline junctions **66** were obtained in high yields (up to 94%) and very high enantioselectivities (up to 99% of *ee*) (Scheme 25) [64]. Dihydroquinoxalin-2-one **65** under the irradiation of visible light and in the presence of Eosin Y and oxygen is oxidized to quinoxalin-2(1*H*)-one (imine).



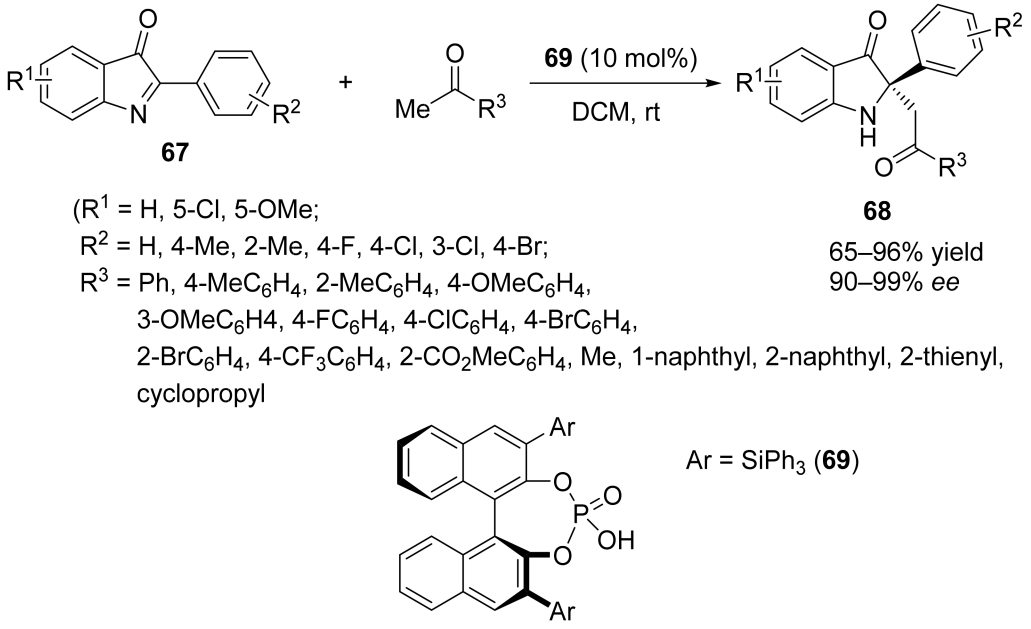
Scheme 25. Mannich reaction of dihydroquinoxalinones with ketones.

In the second case, Guan and He et al. also showed excellent catalytic activity of L-proline in the presence of ruthenium–bipirydyl complex (Scheme 26) [65].



Scheme 26. Synthesis of C2-quaternary indolin-3-ones.

Chiral phosphoric acid **69** was employed as catalysts in asymmetric Mannich reaction of cyclic *C*-acylimines **67** with ketones (Scheme 27) [66]. C2-quaternary indolin-3-ones **68** were formed with excellent values of chemical yield and stereoselectivity [66].

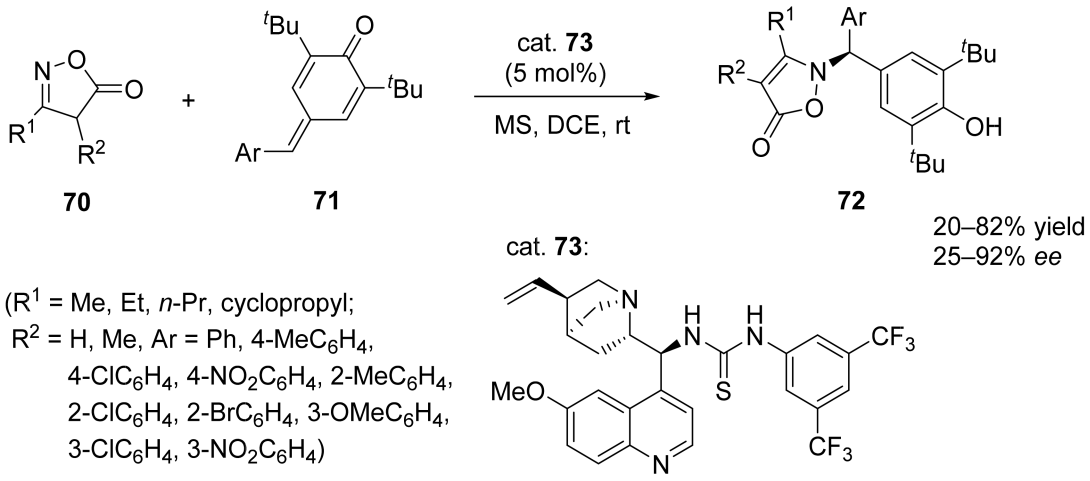


Scheme 27. Mannich reaction catalyzed by chiral phosphoric acid.

5. Asymmetric Michael Reactions

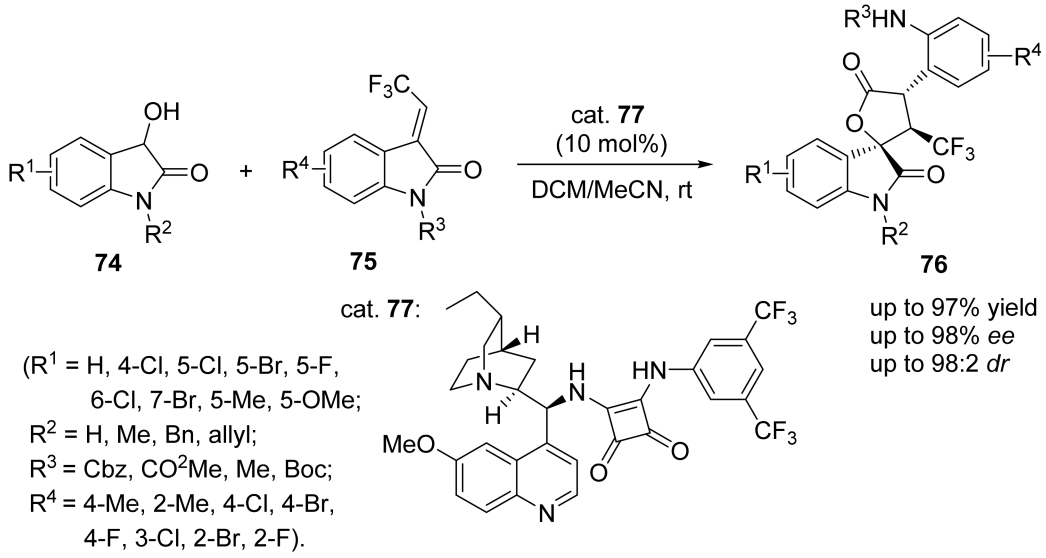
The Michael addition reaction constitutes one of the most powerful tools of construction of C-C bonds in modern synthetic organic chemistry. The number of different Michael donors and acceptors is large and constantly increasing; therefore, this reaction is still the subject of numerous studies. The Michael reaction in the asymmetric version is often a key step in the synthesis of many natural products [67]. The search for new chiral catalysts for this asymmetric transformation is still a challenge for various research groups [68]. Many recent reports inform about the use of bifunctional organocatalysts, such as thiourea–tertiary amine systems [69]. Moreover, Michael additions performed in the presence of zinc ions also enjoy quite a lot of interest [70]. Currently, target materials in the asymmetric Michael addition reaction are very often isoxazole-5-ones and isoxazolidin-5-ones [71], and pyrazolones [72].

Enantioselective 1,6-*aza*-Michael addition reaction of 4*(H)*-isoxazol-5-ones **70** to *p*-quinone methides **71** promoted by various organocatalysts was described by Blay and Pedro et al. [73]. The isoxazol-5-one ring is present in many natural compounds, and there are many examples of compounds from this group that are inhibitors of various enzymes. The properties of this ring mean that some derivatives are successfully used in photonics. The desired isoxazolin-5-one derivatives **72** were formed with the greatest efficiency in dichloroethane (DCE) at room temperature in the presence of 3Å molecular sieves under action of thiourea system **73** (Scheme 28) [73].



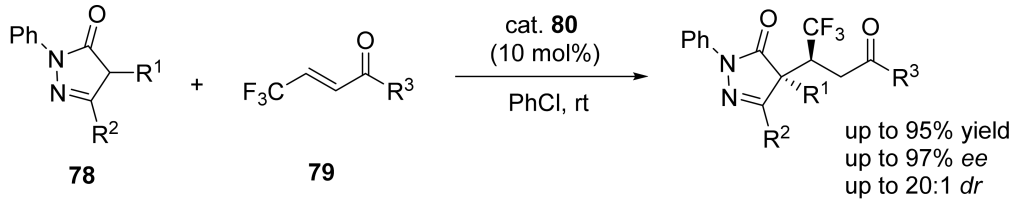
Scheme 28. Enantioselective Michael addition of isoxazolin-5-ones to *p*-quinone methides.

Spirooxindole γ-lactones bearing the CF_3 substituent were synthesized using organocatalytic asymmetric Michael/lactonization cascade [74]. Spiroxoindole lactones have activities such as antibacterial, anti-biofilm or inhibition of (THF)-α-induced apoptosis. 3-Hydroxyindoles **74** reacted with 3-trifluoroethylidene oxindoles **75** in DCM/MeCN mixture at room temperature giving the desired lactones **76** in up to 97% yield, with up to 98:2 of *d.r.*, and with up to 98% *ee* under action of chiral squaramide derivative **77** (Scheme 29) [74].



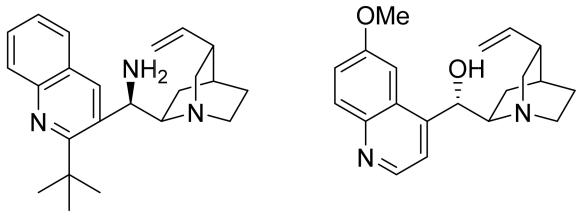
Scheme 29. Synthesis of spirooxindoles γ-lactones.

Highly efficient asymmetric Michael addition of pyrazol-5-ones **78** to β-trifluoromethyl-α,β-unsaturated ketones **79** was reported by Chang et al. (Scheme 30) [75]. Many systems containing a trifluoromethyl group at the stereogenic center are pharmacophores, e.g., Befloxatone is a monoamine oxidase inhibitor, odanacat-ib is a potential drug for osteoporosis by inhibiting the enzyme cathepsin K leading to bone reduction. The highest levels of enantioselectivity and diastereoselectivity of the reaction were achieved using dipeptide-based urea-amide catalyst **80** in chlorobenzene at 25 °C (Scheme 30) [75].



Scheme 30. Michael addition of pyrazol-5-ones to α,β-unsaturated ketones.

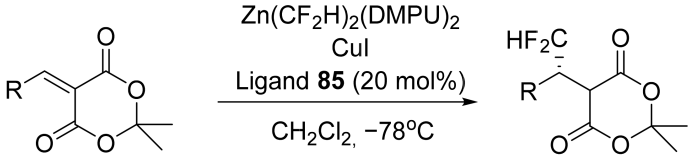
Cinchona-derived aminocatalysts of types **81–82** (Figure 1) were successfully applied in the four-component cycloaddition reaction of 3-substituted 2-cyclopentenones with isoxazole-5-one derivatives [76], and in the Michael reaction of arylidene-isoxazol-5-one with 1,3-diesters [77], respectively.



81 **82**

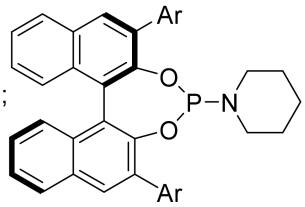
Figure 1. Cinchona-derived catalysts for asymmetric Michael reactions.

Meldrum's acid constitutes a very useful tool in asymmetric organocatalysis including Michael reactions [78]. Chiral P,N-ligands of type **85** were used in the copper-catalyzed enantioselective difluoromethylation of Meldrum's acid derivative **83** using (difluoromethyl)zinc reagents (Scheme 31) [79]. The appropriate β-difluoromethylated carbonyl compounds **84** were formed with enantioselectivities around 80% of *ee* in high to excellent chemical yields [79].



83 **84** up to 99% yield around 80% of *ee*

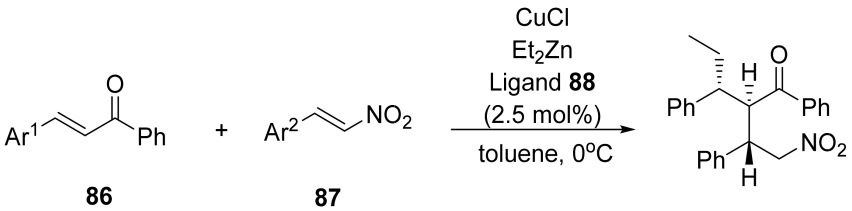
Ligand **85**:



(Ar = 4-methoxy-3,5-*tert*-butylphenyl; R = Ph, 4-$OMeC_6H_4$, 4-ClC_6H_4, 4-$NO_2C_6H_4$, 3,4-$MeOC_6H_3$, 1-naphthyl, isopropyl).

Scheme 31. Asymmetric Michael difluoromethylation of Meldrum's acids.

Chiral P,N-ligands **88** were also used in copper-mediated tandem double Michael reactions of diethylzinc to α,β-unsaturated ketones **86** followed by trapping with nitroalkenes **87** (Scheme 32) [80]. The corresponding tandem products were in high yields and with excellent enantioselectivities [80].

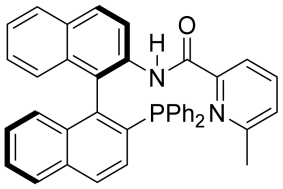


86 **87**

70–85% yield
90–97% *ee*

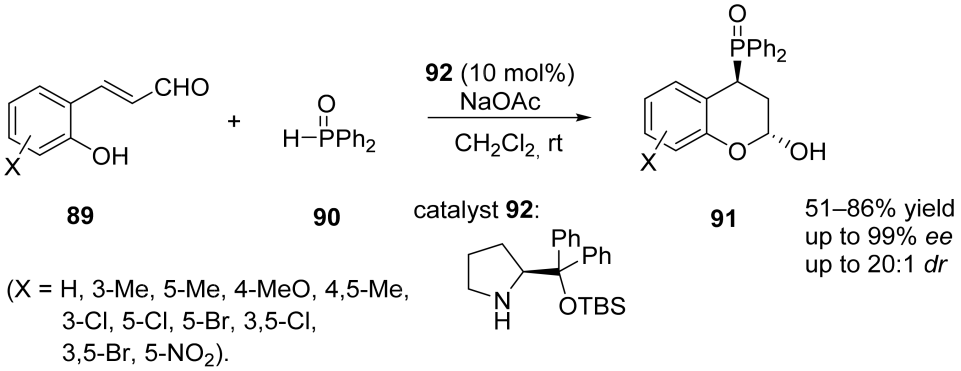
(Ar^1 = Ph, 2-ClC_6H_4, 3-ClC_6H_4, 3-$OMeC_6H_4$, 4-ClC_6H_4, 4-BrC_6H_4, 4-MeC_6H_4, 4-$OMeC_6H_4$, 2-thienyl, 2-furyl, 1-naphthyl; Ar^2 = 3-MeC_6H_4, 3-$OMeC_6H_4$, 4-ClC_6H_4, 4-BrC_6H_4, 4-MeC_6H_4, 4-$OMeC_6H_4$, 2-naphthyl)

Ligand **88**:



Scheme 32. Copper-promoted tandem double Michael reactions.

Diarylprolinol silyl ether **92** was successfully employed in the asymmetric cyclization of *o*-hydroxycinnamaldehydes **89** with diphenylphosphine oxide **90** (Scheme 33) [81]. Organophosphorus compounds are widespread in the natural environment and in many cases have important biological properties. The corresponding 4-diphenylphosphinyl chroman-2-ols **91** were obtained with 84–99% *ee* and 7:1 to 20:1 of diastereomeric ratio [81].



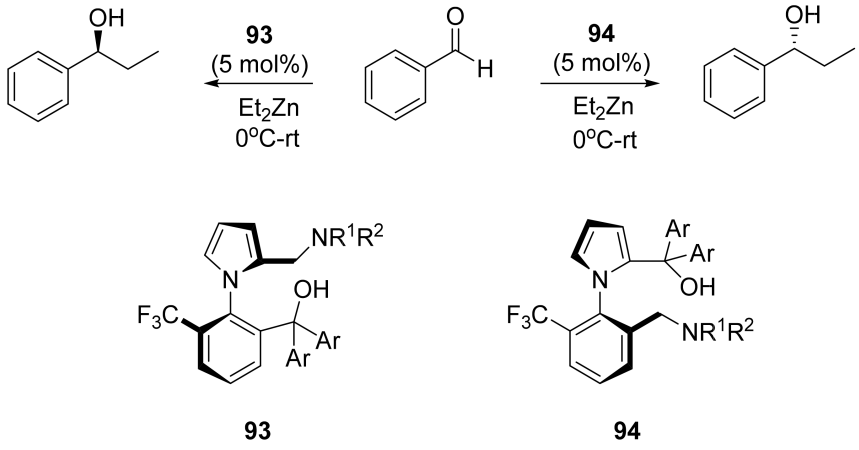
Scheme 33. Cascade cyclization of *o*-hydroxycinnamaldehydes with diphenylphosphine oxide.

Silyl ethers of diarylprolinol were also used in the highly stereoselective synthesis of spiro pyrazolones via Michael/Conia-ene cascade reaction [82] and in the synthesis of biaryl atropoisomers via domino Michael–Henry reaction affording the substituted nitrocyclohexanecarbaldehydes [83].

6. Asymmetric Reactions in the Presence of Zinc Ions

Among the very wide range of asymmetric reactions taking place in the presence of zinc ions, the most exploited but still valid and simple reactions are asymmetric additions of diethylzinc to carbonyl compounds, especially aldehydes. In 2018, Wang described an enantioselective analysis towards the rational design of chiral ligands efficiently catalyzing the asymmetric addition of diethylzinc to benzaldehyde [84].

The effect of regioisomerism on the efficiency of amino alcohol ligands in the asymmetric addition of diethylzinc to benzaldehyde was investigated by Mátravölgyi et al. [85]. The aforementioned reactions performed in the presence of atropisomeric 1-phenylpyrroles **93** and **94** led to the opposite enantiomers of desired alcohol with high enantioselectivity (Scheme 34) [85].



Scheme 34. Addition of Et_2Zn to benzaldehyde in the presence of atropisomeric 1-phenylpyrroles.

Recent developments towards efficient, highly enantioselective addition of diethylzinc to aldehydes include the use of chiral derivatives such as (Figure 2): 5-*cis*-substituted proline derivatives (prolinols **95** and prolinamines **96**) [86], proline-based *N*,*N*-dioxides **97** [87], pinane-based tridentate ligands **98** [88], axially chiral tridentate isoquinoline-derived ligands **99** [89], chiral oxazoline-based systems **100** [90], thiophene-derived amino alcohols **101** [91], amino alcohols **102** [92], noscapine-derived β-amino alcohols **103** [93,94], chiral ferrocene and ruthenocene substituted aminomethylnaphthols **104** [95], and chiral P,N-ligands **105** [96].

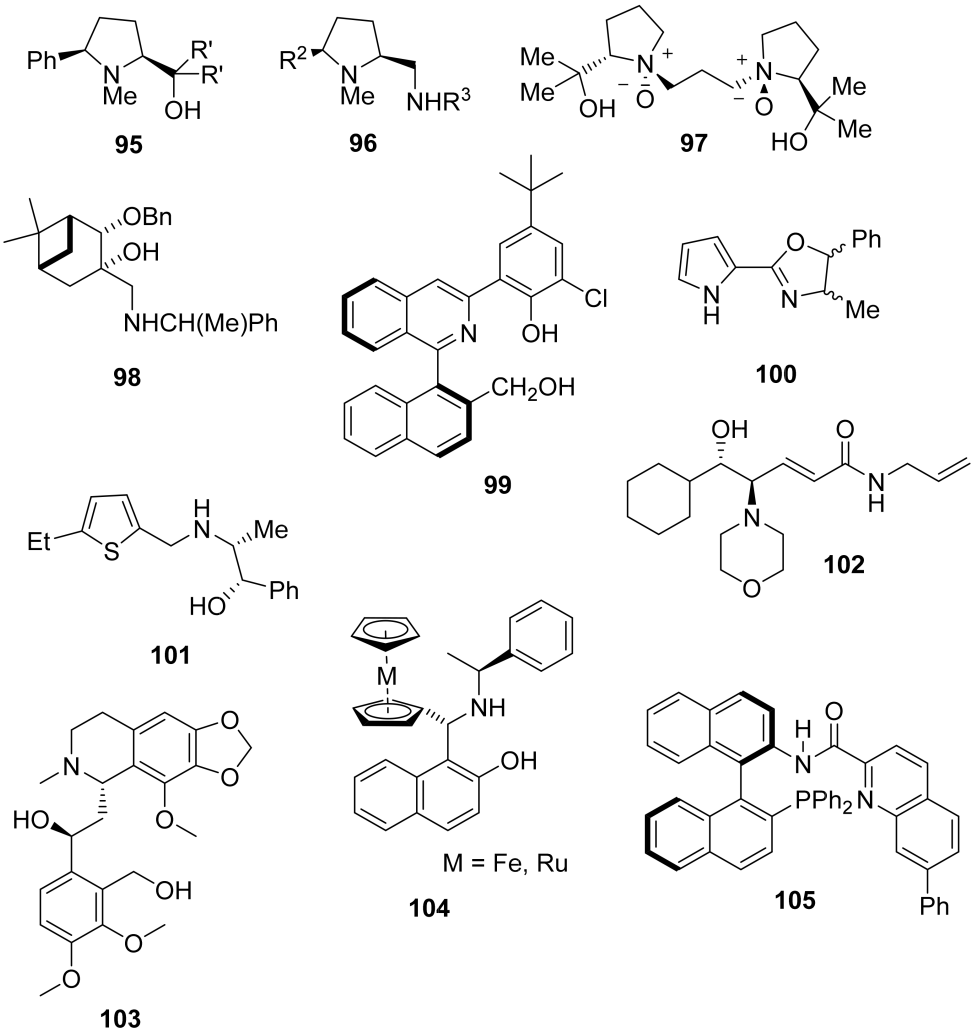
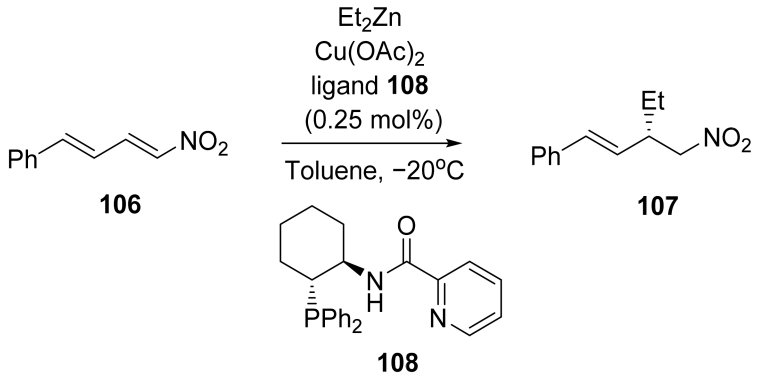


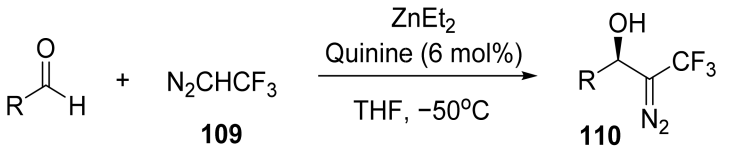
Figure 2. Catalysts for asymmetric diethylzinc addition to aldehydes.

Enantioselective copper(II)-promoted 1,4-conjugate addition of Et_2Zn to nitrodienes **106** was reported by Wu et al. [97]. The corresponding 1,4-adducts **107** were obtained in 81–98% yield and with 87–97% *ee* when a chiral amidophosphine ligand **108** was applied (Scheme 35) [97].



Scheme 35. Enantioselective addition of diethylzinc to nitrodienes.

Enantioselective aldol-type reaction of trifluorodiazomethane **109** with various aldehydes was efficiently catalyzed by quinine in the presence of diethylzinc in THF (Scheme 36) [98]. The corresponding chiral β-trifluoromethyl alcohols **110** were constructed in very satisfactory levels of yield and enantioselectivity [98].



(R = 2-naphthyl, Ph, 4-MeC_6H_4, 3-MeC_6H_4, 2-MeC_6H_4, 4-$MeOC_6H_4$, 3-$MeOC_6H_4$, 3-$PhOC_6H_4$, 4-FC_6H_4, 3-ClC_6H_4, 2-ClC_6H_4, 4-BrC_6H_4, 2-BrC_6H_4, 4-IC_6H_4, 4-$CF_3C_6H_4$, 4-$NO_2C_6H_4$, 2$NO_2C_6H_4$, 4-$CO_2MeC_6H_4$, 3,4-ClC_6H_3, 1,3,5-MeC_6H_2, 1-naphthyl, 2-furyl, 2-thienyl, 3-pirydynyl)

Scheme 36. Enantioselective aldol-type reaction of CF_3CHN_2 with aldehydes.

7. Summary

This review article presented selected examples of recent achievements in the field of asymmetric synthesis with chiral catalysts. The authors' attention was focused on asymmetric transformations such as the cyclopropanation, Friedel–Crafts, Mannich, Michael reactions, and reactions in the presence of zinc ions. All the examples given relate to reactions with high chemical yields and high stereoselectivity.

The research related to asymmetric synthesis with the use of chiral organic catalysts is extremely well studied and is constantly developed by many research groups around the world. The asymmetric reactions presented in this review are well known and exploited in the literature. Our suggestion for future research directions in this field is that researchers should focus on less obvious asymmetric transformations, such as Morita–Baylis–Hillman or Rauhut–Currier reactions, whose chiral products have potential applications in many fields. Moreover, perhaps it is worth trying to design chiral catalysts taking into account new structural motifs, such as the aziridine ring.

Author Contributions: Conceptualization, M.R. and S.L.; software, A.B.-S. and M.R.; formal analysis, M.R. and S.L.; writing—original draft preparation, M.R. and A.B.-S.; writing—review and editing, M.R. and S.L. All authors have read and agreed to the published version of the manuscript.

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