Chapter

# Catalytic Enantioselective Reactions of Biomass-Derived Furans

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## Abstract

In this chapter, recent developments with regard to catalytic enantioselective reactions of furans, derived from biomass such as unsubstituted furan, 2-methylfuran, 2,5-dimethylfuran, and furfural are described. Although several review articles have dealt with the Diels-Alder reactions of furans, there have been no articles highlighting enantioselective versions. The resulting products derived from the catalytic enantioselective reaction of furan are often found as core structures in natural products and pharmaceuticals with important pharmacological activities. After recognizing the valuable skeleton of chiral furan derivatives, numerous attempts have been made to synthesize them by utilizing enantioselective cycloaddition reactions, Friedel-Crafts reactions, and nucleophilic addition reactions. Enantioselective cyclization reactions using furans as the 4π diene component provided chiral dihydrofuran derivatives. On the other hand, Friedel-Crafts and nucleophilic addition reactions served various furan derivatives with a chiral carbon atom in the α-position.

**Keywords:** enantioselective, cycloaddition, Diels-Alder, Friedel-Crafts, furan, nucleophilic addition

## 1. Introduction

Furfural and 5-hydroxymethylfurfural (HMF) have received significant attention as promising platform chemicals due to their versatile utility in the synthesis of various commodity chemicals and fuels [1–3]. These platform chemicals can be easily transformed into value-added chemicals, such as 2-methylfuran, 2,5-dimethylfuran, and other furans via chemical conversions or fermentation [4–6]. Since aromatic heterocycle furans are present in a variety of chiral natural products, pharmaceuticals, and other intermediates, a plethora of enantioselective methodologies has been developed for the synthetic community [7–9]. The important strategies are given as follows—(i) enantioselective cyclization reactions including cycloadditions using furans as the 4π diene component and cyclopropanation between furan and diazoester to obtain various valuable chiral synthons (Section 2); (ii) enantioselective Friedel-Crafts cycloadditions for the fabrication of carbon-carbon bonds between furans and electron-deficient alkenes, yielding chiral centers at the α- or β-position of furans (Section 3); (iii) various enantioselective nucleophilic addition reactions of furfural as an electrophile for the construction of chiral

hydroxyl functional groups (Section 4). Thus, this chapter is divided into three sections.

## 2. Catalytic asymmetric cyclization reactions of furans

Since the first cyclopropanation between unsubstituted furan and chlorodiazopropene was reported by de Meujere and Kositkov in 1991, reactions using unfunctionalized furan have emerged as a challenging area in organic chemistry [10]. In most cases, numerous reports have utilized substituted furan at the 2- or 3-positions. However, biomass-derived furan such as normal furan or methyl-substituted furans are generally held to be poor dienes in Diels-Alder reactions and have poor reactivity for cyclization as well as cyclopropanation. Therefore, it has been difficult to develop such reactions with simple furan, and extending it to the catalytic enantioselective version was extremely difficult. Since the discovery of an enantioselective furan Diels-Alder reaction in 1997 by the Evans group [11], some progress in this area has been achieved. The aim of this chapter is to mainly discuss the catalytic enantioselective reaction of simple furans for Diels-Alder reaction, [4 + 3] cyclization, and cyclopropanation. The reaction of functionalized and substituted furan will not be included here.

### 2.1 Cu or Pd-catalyzed enantioselective Diels-Alder reactions with furans

The first highly enantioselective catalytic Diels-Alder reaction using an unsubstituted furan reactant was accomplished by the Evans group in 1997 [12, 13]. They utilized a bisoxazoline-copper complex **1** as a Lewis acid catalyst for the Diels-Alder reaction between acrylamide **3** and furan **2** to produce the chiral cycloadduct products **4** as an important synthetic intermediate of shikimic acid in 97% yield with 97% ee (**Figure 1**).

The Diels-Alder reaction between acrylamide **3** and furan **2** was accomplished using different metal catalysts. The Lassaletta and Ishihara groups independently reported copper(II) complex-catalyzed Diels-Alder reactions to produce the *endo*-selective cycloadduct product **8** in 92% yield with 98% ee and 88% yield with 96% ee, respectively [14, 15]. An *exo*-selective and highly enantioselective Diels-Alder reaction of acrylamide **3** and furan **2** were accomplished by the Kabuto group in 2004 through the use of a chiral phosphinooxazolidine-palladium complex **7** as the active catalyst (**Figure 2**) [16].

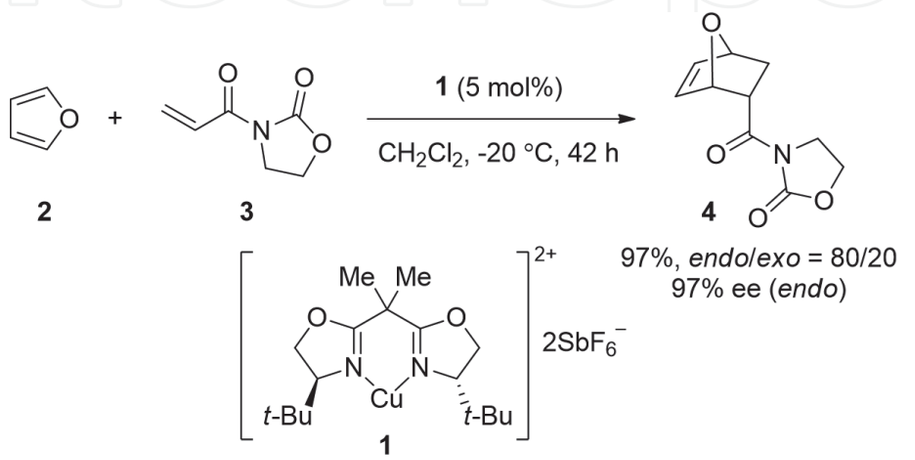


**Figure 1.**
*Catalytic enantioselective Diels-Alder reactions with copper catalyst.*

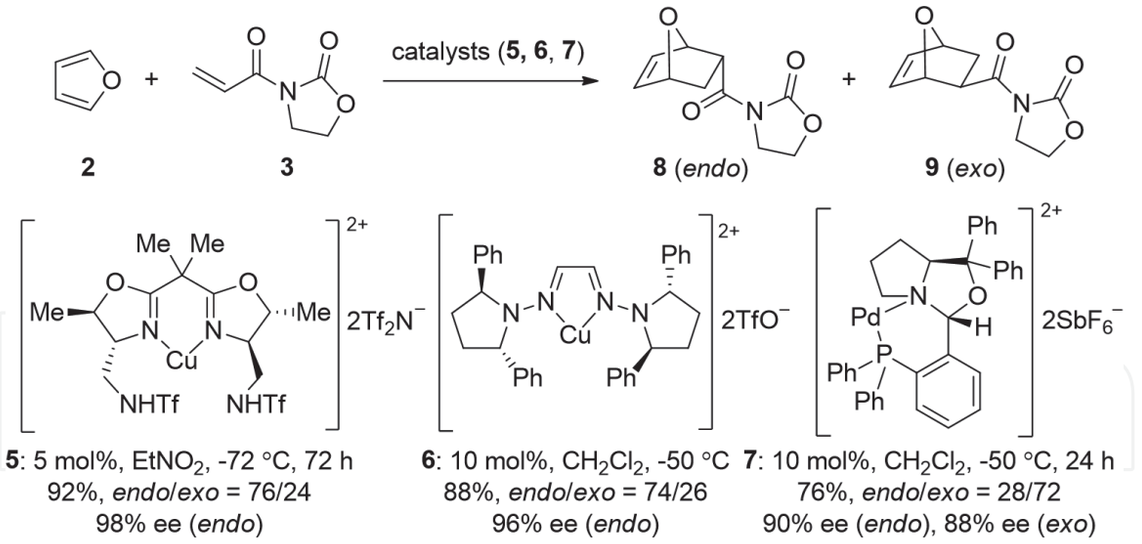


**Figure 2.**
*Chiral copper or palladium catalyst for the catalyzed Diels-Alder reaction.*

## 2.2 Oxazaborolidium-catalyzed enantioselective Diels-Alder reactions with furans

A few examples of catalytic asymmetric Diels-Alder reaction of unsubstituted furans have been reported. Corey, Ryu, and coworkers successfully reported the Diels-Alder reaction between furan **12** and 1,1,1-trifluoroethyl acrylate **3** through the use of oxazaborolidinium **10** or **11** as a metal-free catalyst in combination with trifluoroacetic acid (TFA) or bis(trifluoromethane)sulfonimide ($Tf_2NH$) (**Figure 3**) [17]. Various methyl-substituted furans were employed as dienes, which exhibited superior activity and tolerance for this study, rendering the desired cycloadduct product **13** in excellent yields with excellent diastereo- and enantioselectivities.

In 2011, Shibatomi and coworkers accomplished chiral oxazaborolidine **15**-catalyzed enantioselective Diels-Alder reactions between furan **12** and fluoromethylated (*E*)- or (*Z*)-acrylate yielding the corresponding product **17** with up to 99% ee (**Figure 4**) [18]. As depicted in **Figure 4**, various β-fluoro-substituted

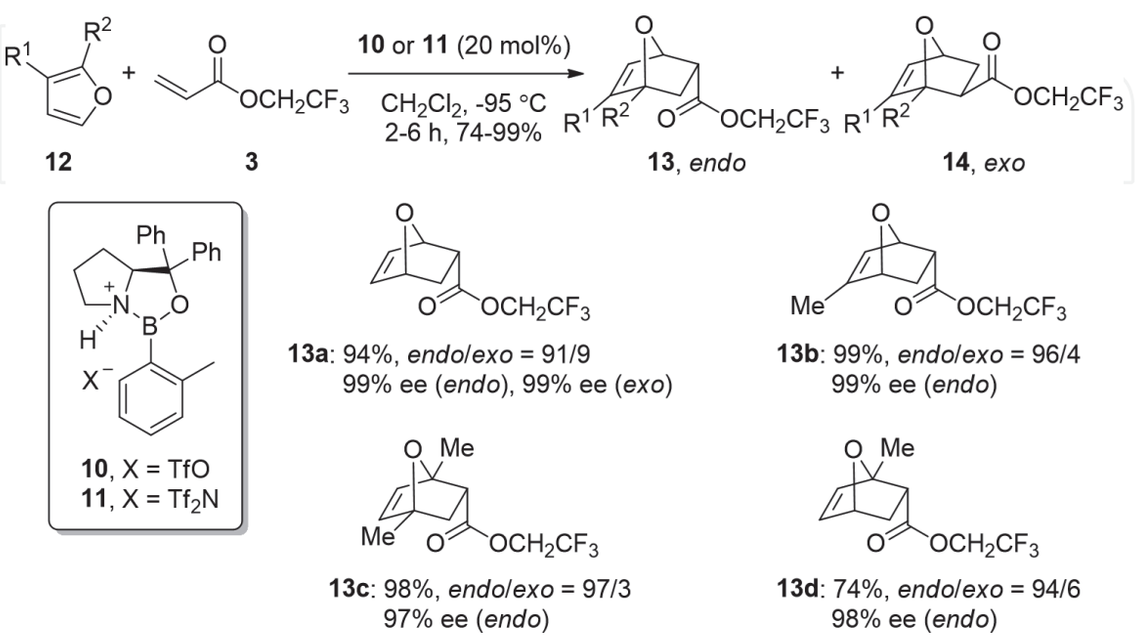


**Figure 3.**
*Enantioselective Diels-Alder reactions with 1,1,1-trifluoroethyl acrylate.*

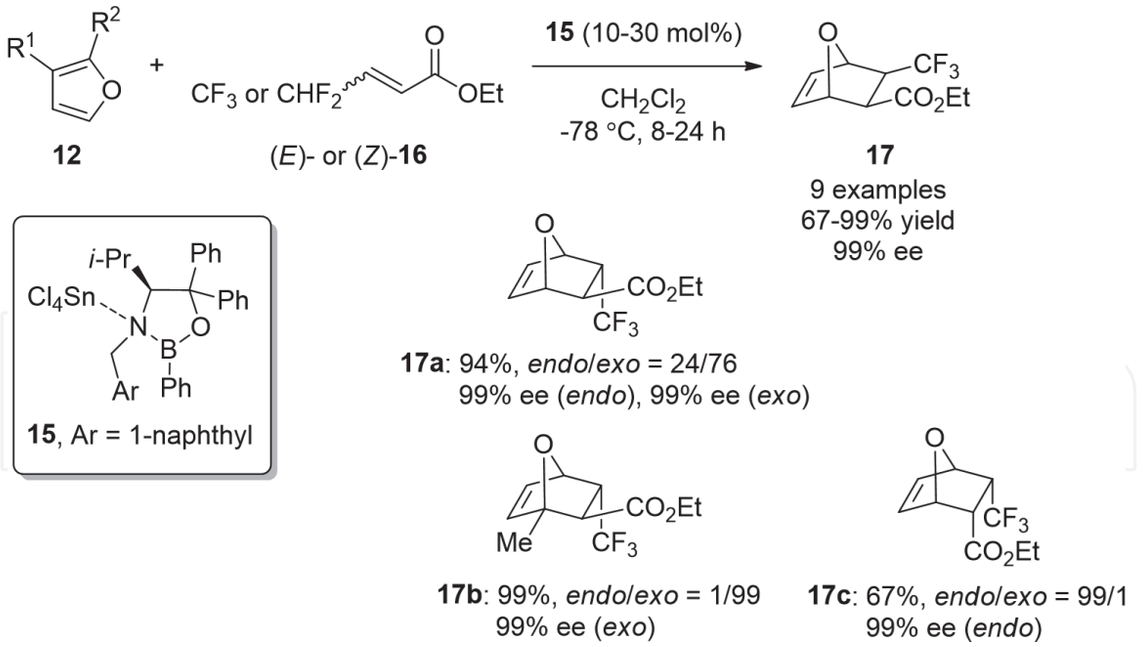


**Figure 4.**
exo-*Selective enantioselective Diels-Alder reaction with fluoromethylated acrylate.*

(*E*)- or (*Z*)-acrylates **16** and substituted furans **12** were well tolerant with a selective approach for high enantioselectivities as well as *endo*/*exo*-selectivities (up to 99/1 and 1/99).

Corey and coworkers reported asymmetric Diels-Alder reactions of di-substituted furans **20** with acrylate **21** in 2016 [19]. The use of oxazaborolidinium catalyst **18** activated by aluminum bromide ($AlBr_3$) gave the cycloadduct **22** in 99% yield with 99% ee (**Figure 5**). Diastereoselectivity and reaction times were further improved through the introduction of fluorinated oxazaborolidines as second-generation catalyst **19**.

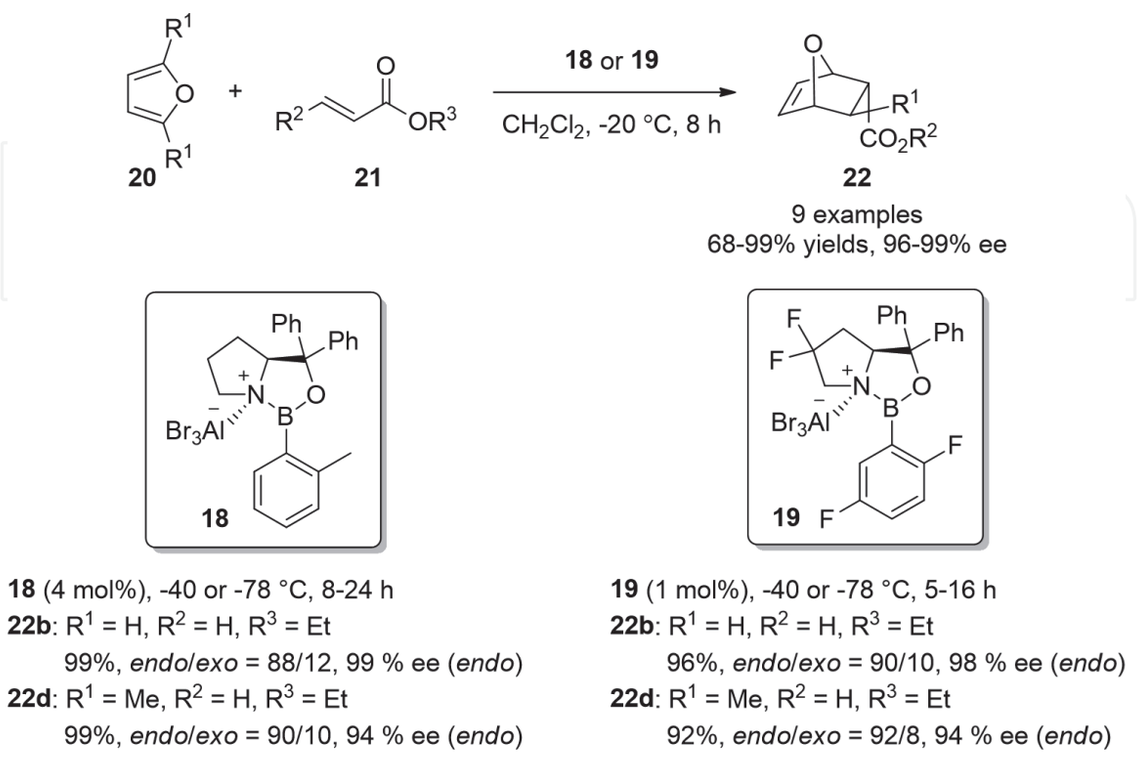


**Figure 5.**
*Enantioselective Diels-Alder reactions with various dienophiles.*

Occasionally, the catalytic system comprising a chiral *N*-heterocyclic stabilized borenium cation for the enantioselective Diels-Alder reaction required low reaction temperatures. To overcome this drawback, Chein and coworkers designed a sulfur-stabilized borenium cation, oxathiaborolium catalyst **23** in combination with tin chloride ($SnCl_4$). However, in the case of unsubstituted furan **2**, the reaction required −60 °C for the enantioselective Diels-Alder reaction with ethyl acrylate **24** (**Figure 6**) [20].

In 2010, Corey and coworkers reported a catalytic asymmetric Diels-Alder reaction by employing an allenic ester **26** as the dienophile with di-substituted furans **20**. The use of 5–20 mol% of chiral oxazaborolidinium ion (COBI) **11** or **18** as a catalyst gave various synthetically valuable cycloadducts **27** with good to excellent yields and high stereoselectivities (**Figure 7**) [21].

The usefulness of the Diels-Alder cycloadduct **27a** is illustrated in **Figure 8**. Selective reduction of **27a** and hydrogenation using Wilkinson's catalyst produced synthetic unit **28**. Further transformation of **28** to (−)-laurenditerpenol, known to be a potent inhibitor of HIF-1α, was achieved based on a known procedure [22].

An alternative organocatalytic Diels-Alder reaction of furan **2** with acrylic enone **29** was developed by the Harada group. *Allo*-Threonine-derived oxazaborolidinones (OXB) **28** were employed as a catalyst to afford the corresponding cycloadduct **30** with good to high yields and excellent enantioselectivities (**Figure 9**) [23]. Although this new motif catalyst **28** has weaker Lewis acidity compared to the cationic

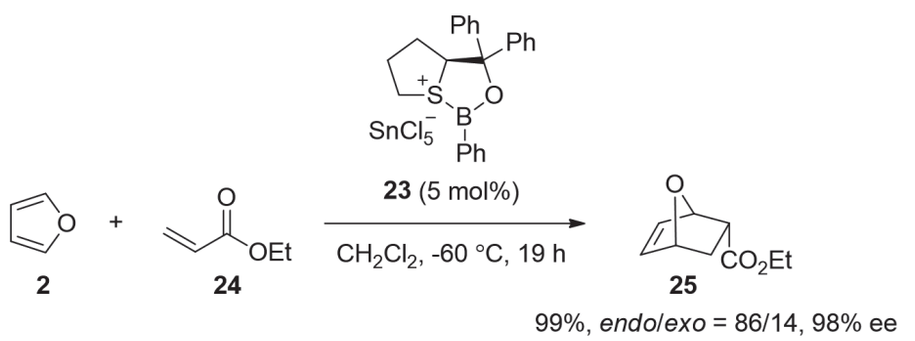


**Figure 6.**
*Enantioselective Diels-Alder reactions with ethyl acrylate.*

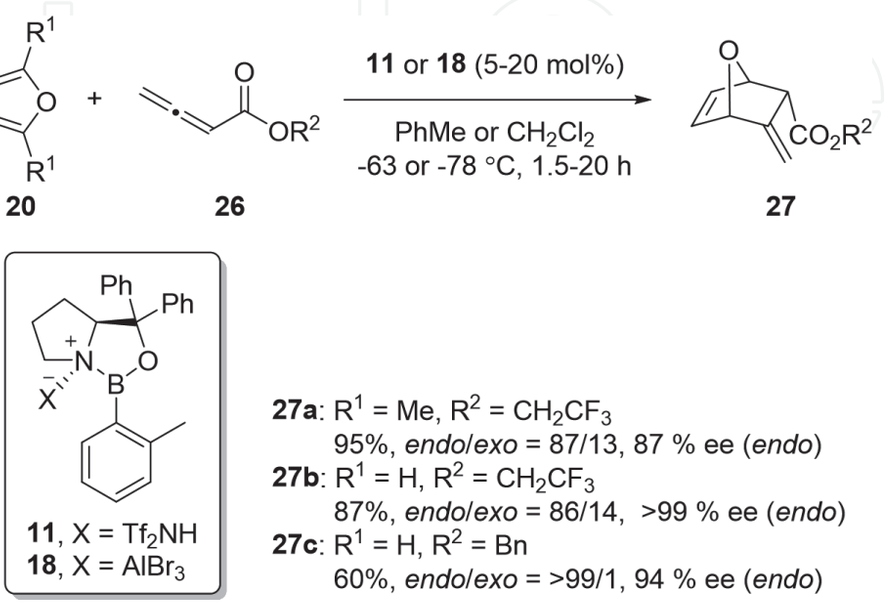


**Figure 7.**
*Enantioselective Diels-Alder reactions with allenic ester.*

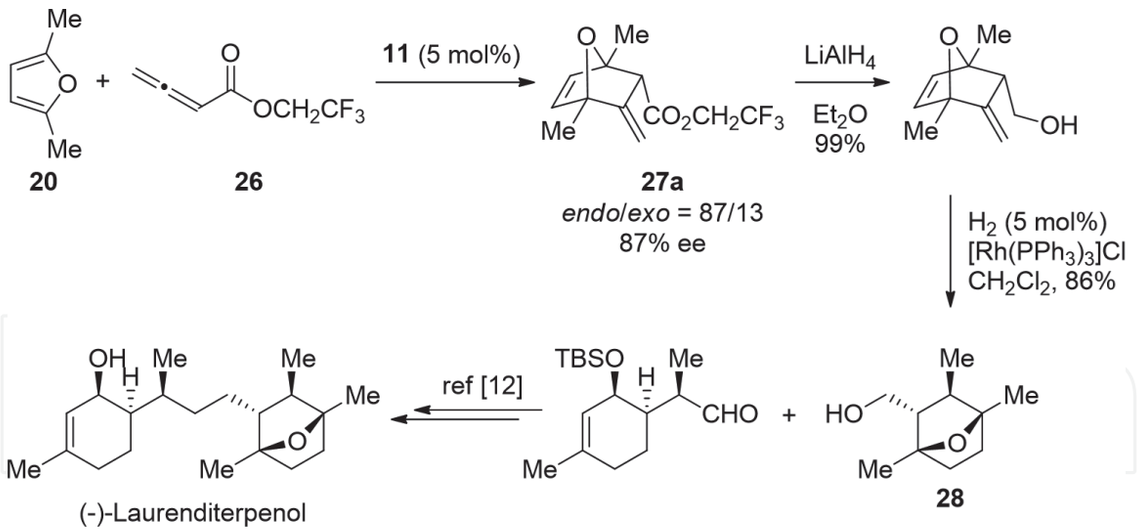


**Figure 8.**
*Synthesis of (−)-lauenditerpenol.*

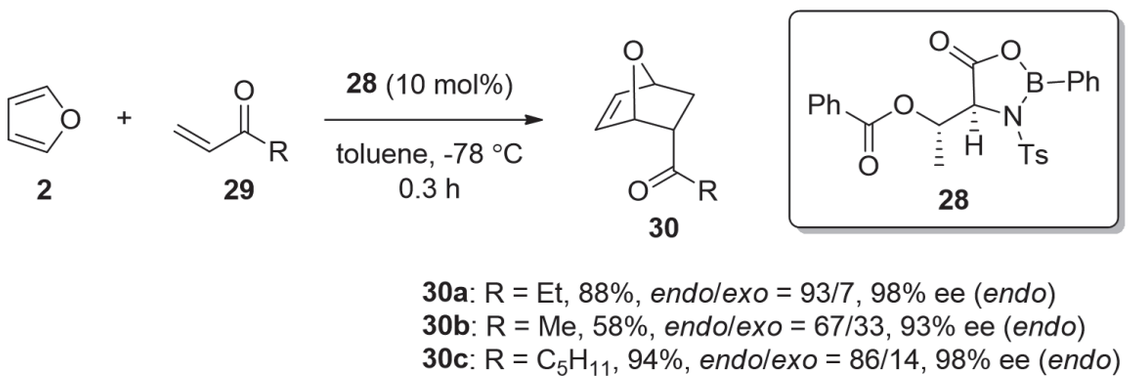


**Figure 9.**
*Chiral Diels-Alder reactions with α,β-unsaturated ketones catalyzed by oxazoborolidinone.*

oxazaborolidine catalyst, OXB catalyst **28** exhibited high performance in terms of stereoselectivity in Diels-Alder reactions between furans and α,β-unsaturated ketones.

### 2.3 Enantioselective [4 + 3] cyclization (or annulation) reactions with furans

The [4 + 3]-annulation consisting of the tandem cyclopropanation/Cope rearrangement of furan is a useful and predictable tool for the stereoselective synthesis of seven-membered rings. Asymmetric synthesis of 8-oxabicyclo[3.2.1] octene derivatives (**33** or **34**) was achieved by utilizing vinyl diazoacetate **31** or **32** bearing chiral auxiliaries, such as (*S*)-lactate or (*R*)-pantolactone, respectively, in the presence of catalytic amounts of rhodium(II) octanoate. Practical and general [3 + 4]-annulation methods for the synthesis of oxabicyclic product with excellent yields (up to 91% yield) and enantioselectivities (up to 95% ee) were developed by Davies and coworkers in 1996 (**Figure 10**) [24].

In 2008, the same group described the Tetrakis[(*R*)-(+)-*N*-(*p*-dodecylphenylsulfonyl)prolinato]dirhodium(II) ($Rh_2$(*R*-DOSP)$_4$)-catalyzed reaction of vinyl diazoacetate **35** and furan **36** for the generation of formal [4 + 3] cycloadducts **37** with excellent stereoselectivities (up to >94% de and 98% ee). This reaction was smoothly proceeded by a tandem cyclopropanation/Cope rearrangement followed by stereoselective tautomerization (**Figure 11**) [25].

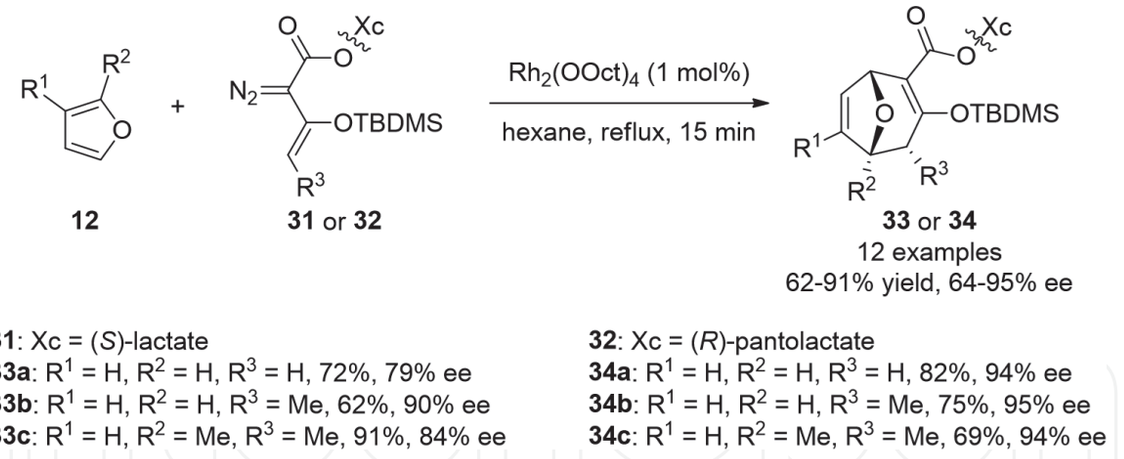


**Figure 10.**
*Enantioselective [4 + 3] cyclization with chiral auxiliary substituted diazoacetoacetate.*

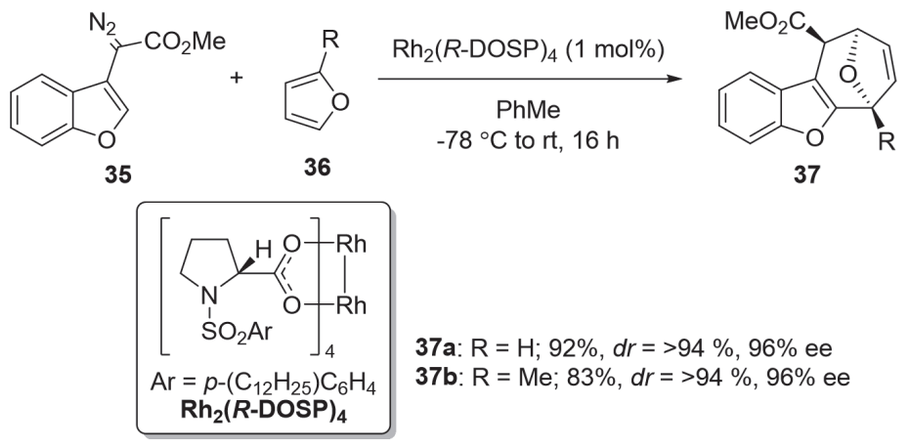


**Figure 11.**
*Enantioselective [4 + 3] cycloaddition with benzofuranyldiazoacetates.*

In 2017, Vicario and coworkers reported that chiral 1,1-binaphthol (BINOL)-based Brønsted acid **38** catalyzed the enantioselective oxidative [4 + 3] cycloaddition of furan **40** and oxyallyl cation generated *in situ* through the oxidation of allenamide **39** with dimethyldioxirane (DMDO) as the oxidant. Stereochemical environments were induced through hydrogen-bonding and ion-pairing interactions during the [4 + 3] cycloaddition process, enabling efficient chirality transfer that furnished [4 + 3] cycloaddition products **41** in excellent yields and with high stereocontrol (**Figure 12**) [25].

In 2017, Jacobsen and coworkers reported that H-bond donors such as chiral squaramide **42** could activate relatively unreactive electrophiles for promoting enantioselective reactions in the following manner. Initially, chiral squaramide was able to interact with silyl triflates by binding the triflate counterion to produce a highly Lewis acidic complex (so-called enhanced Lewis acidity). The silyl triflate-chiral squaramide combination promoted the generation of oxocarbenium intermediates from acetal **43**. Controlled enantioselectivity during the nucleophilic addition of furan **40** to the cationic intermediate was achieved through noncovalent interactions between the squaramide catalyst and the oxocarbenium triflate. Under optimal reaction conditions, the cycloadducts **44** could be obtained in 55–98% yields with 66–96% ee (**Figure 13**) [26].

### 2.4 Enantioselective cyclopropanation reactions with furans

Reactions of furans with carbenoids led to cyclized reactions, such as cyclopropanation. Additionally, a cyclopropanation reaction could be performed through

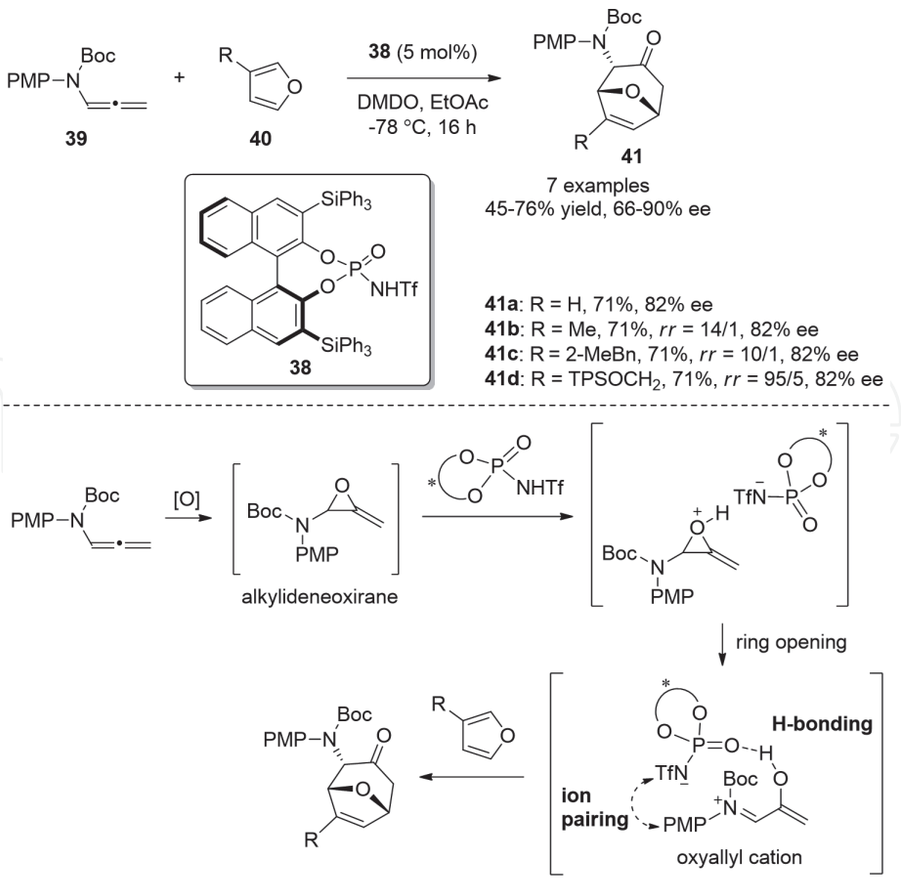


**Figure 12.**
*Enantioselective [4 + 3] cyclization with allenamide.*

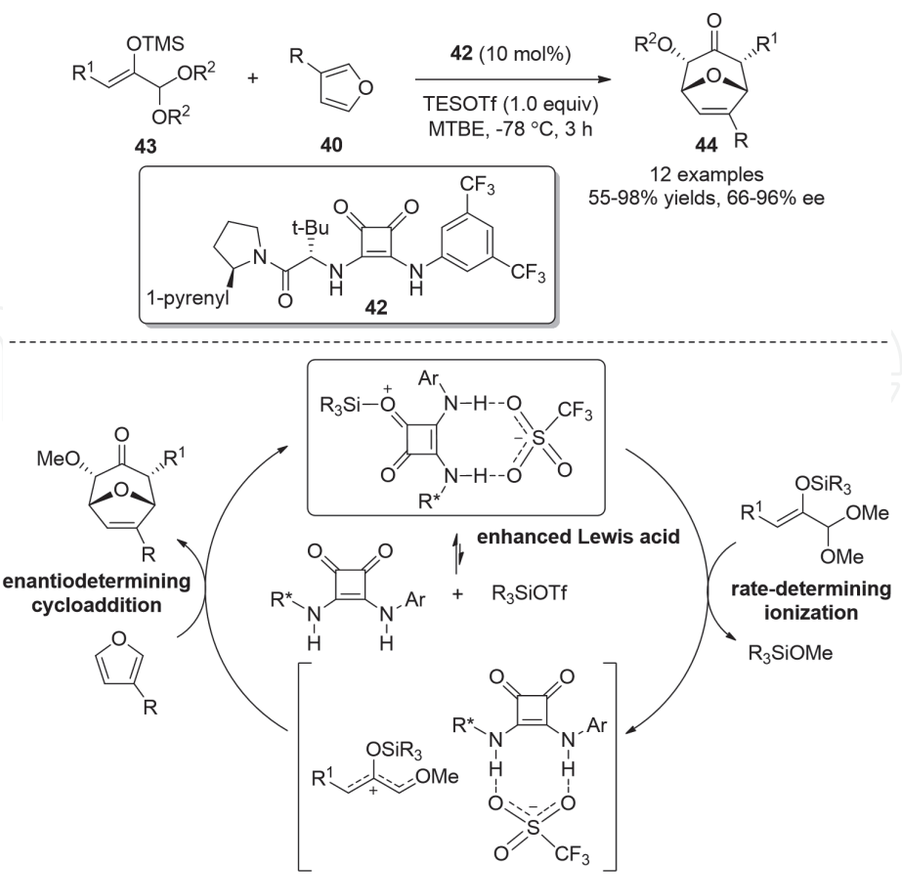


**Figure 13.**
*Enantioselective [4 + 3] cyclization with silyl enol ether.*

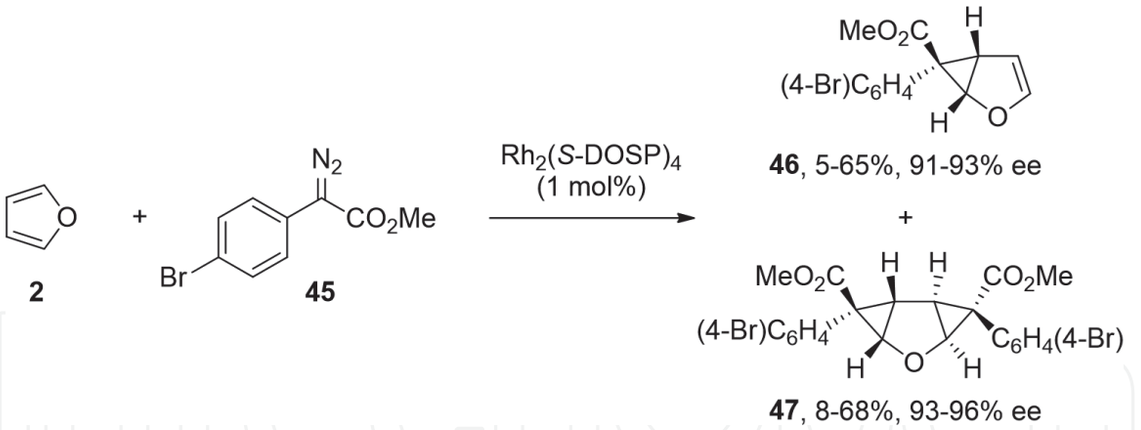


**Figure 14.**
*Enantioselective cyclopropanation with vinyldiazoacetates.*

the reaction of furan and diazoacetate under a metal catalyst. Reiser and coworkers reported the enantioselective cyclopropanation of furans using a copper catalyst, however, the reaction was achieved when the furan was substituted with ester groups at the 2- or 3-position [27]. To solve this problem, Davies and coworkers designed the catalytic system using dirhodium catalyst. When simple furan and aryl diazoester was subjected to the rhodium-catalyzed enantioselective cyclopropanation reaction, both cycloadduct product **46** and bis-cyclopropanation product **47** were obtained in 5–65% yields with 91–93% ee and 8–68% yields, 93–96% ee, respectively (**Figure 14**) [28].

## 3. Catalytic asymmetric Friedel-Crafts reactions of furans

One of the most efficient methods for the synthesis of chiral heteroaromatic compounds with a stereogenic center in the benzylic position is the Friedel-Crafts reaction between carbonyl compounds and electron-deficient alkenes [29]. This field of chemistry has been intensely explored since around 2000, and interest in this field is still growing. Most catalytic enantioselective Friedel-Crafts reactions can be utilized with electron-rich aromatic and heteroaromatic compounds, such as aniline and indole derivatives. However, reports with regard to the use of furans for this study are still scarce due to the relative instability and reduced nucleophilicity of furans compared to indoles and pyrroles [30]. In particular, catalytic enantioselective versions of the Friedel-Crafts reaction with biomass-derived furans as well as normal furan are much less developed than other aromatics.

The first catalytic enantioselective Friedel-Crafts reaction using biomass-derived furan was accomplished by the Jørgensen group in 2000 [31]. Only methyl or trimethylsilyl-substituted furans **36** were subjected to the Friedel-Crafts reaction in combination with ethyl glyoxalate **49** in the presence of the C2-symmetric chiral Cu(II)-bis(oxazoline) complexes **48** as the catalyst, resulting in the formation of the desired product **50** in low to high yields with moderated enantioselectivities (**Figure 15**).

One year later, in 2001, the same group described an enantioselective Friedel-Crafts reaction of normal furan or biomass-derived furans **36** with ethyl trifluoropyruvate **51** utilizing the chiral Cu(II)-bis(oxazoline) complex **48** [32]. In the case of non-substituted furan, a poor yield (15%) for the Friedel-Crafts product **52** was observed despite achieving good enantioselectivity (81% ee). However, various substituted furans provided the desired products with good to high enantioselectivities (**Figure 16**).

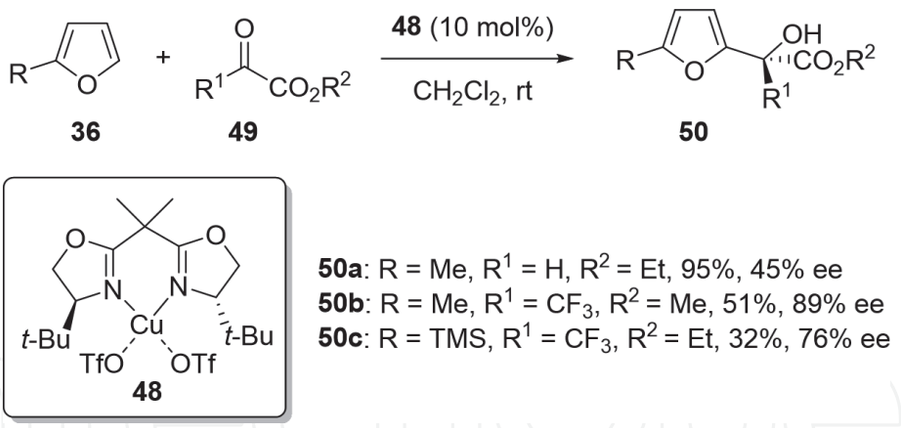


**Figure 15.**
*Enantioselective Friedel-Crafts reactions with glyoxalates.*

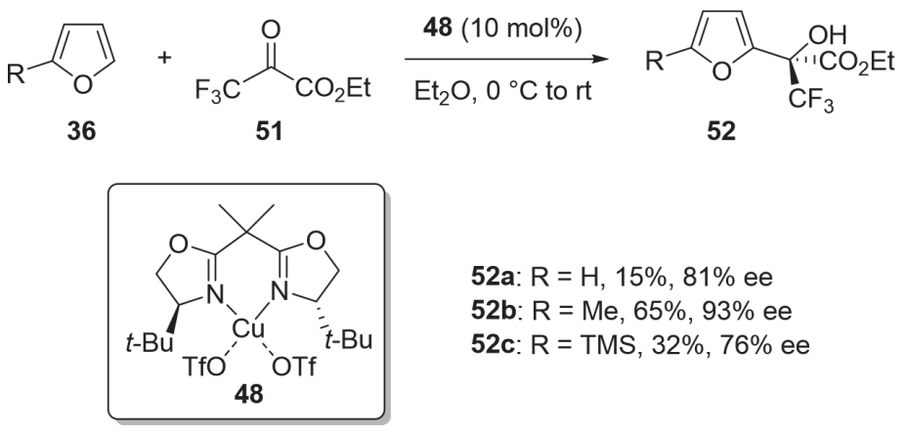


**Figure 16.**
*Enantioselective Friedel-Crafts reactions with ethyl trifluoropyruvate.*

In 2009, Yamazaki and coworkers utilized chiral *cis*-aminoindanol-derived bis (oxazoline)-Cu(II) complexes in catalytic enantioselective Friedel-Crafts reactions between furans **12** and ethenetricarboxylates **54**. As a result, chiral 2-alkylated products **55** were obtained in high yields (73–93) with low to moderate enantioselectivities (25–62% ee) (**Figure 17**) [33].

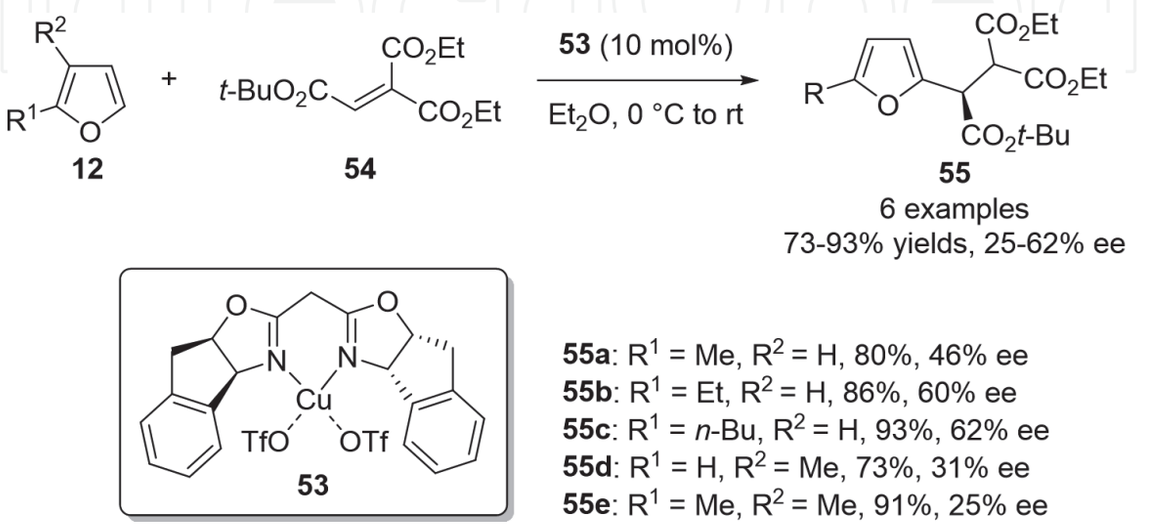


**Figure 17.**
*Enantioselective Friedel-Crafts reactions with ethenetricarboxylates.*

Another attempt with regard to the asymmetric Friedel-Crafts reaction of furans **36** with alkyl glyoxalates **57** utilizing Jacobsen's Co(II)-salen complexes **56** as a catalyst was accomplished by the Jurczak group in 2006 (**Figure 18**) [34]. High-pressure (ca. 10 kbar) conditions were essential to obtain chiral furfuryl alcohols **58** as an important synthetic intermediate in moderate to good yields (28–85%) with moderate enantioselectivities (26–66% ee).

A few years later, in 2008, the same group successfully performed catalytic enantioselective Friedel-Crafts reaction between furans **36** and *n*-butyl glyoxalates **60** by switching the catalytic system from Co(II)-salen complexes **56** to BINOL/Ti complexes **59**. As a result, the enantioselectivity and chemical yield of the desired chiral furanyl hydroxyacetate **61** were enhanced compared to the previous results in **Figure 18**. Notably, various substituted furans including normal furan **36** were tolerant for this reaction and provided the desired products **61** in excellent yields with high to excellent enantioselectivities (**Figure 19**) [35].

Cationic square planar metal complexes $[M(diphosphine)]^{2+}$, where M = Pt, Pd, Ni)] have emerged as an alternative class of Lewis acid catalysts such as

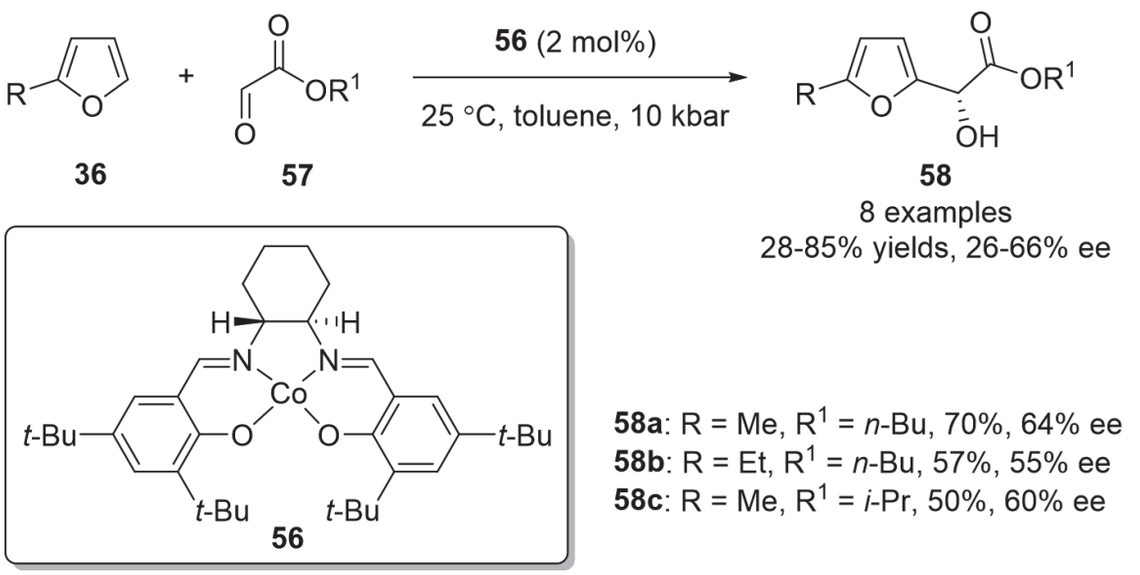


**Figure 18.**
*Enantioselective Friedel-Crafts reactions with alkyl glyoxalates.*

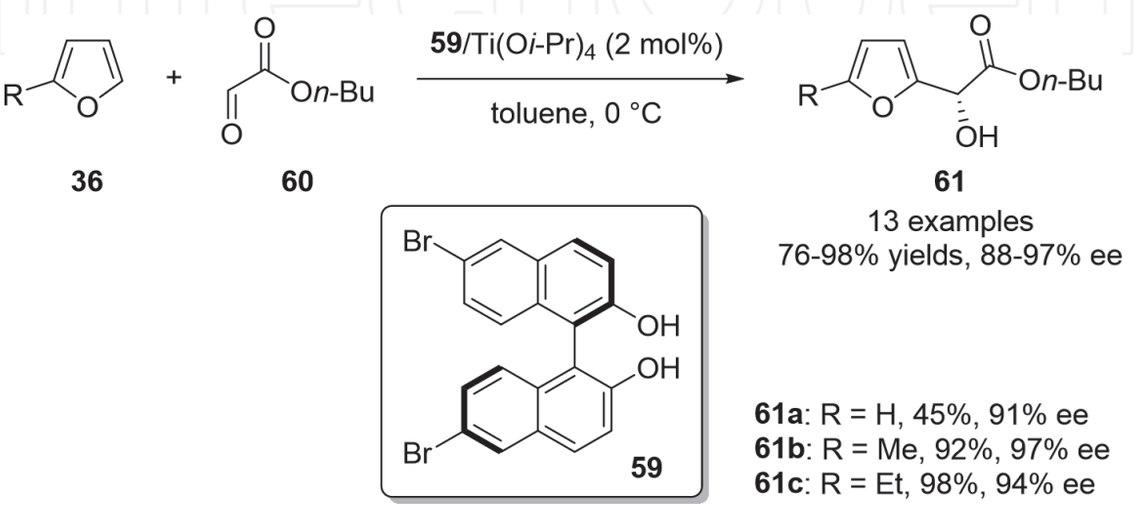


**Figure 19.**
*Enantioselective Friedel-Crafts reactions with* n*-butyl glyoxalates.*

Cu-bisoxazolines (Box), Ti-BINOL, and Co-salen due to the following unique characteristics—(i) well-defined coordination geometries to help control the stereochemical environment; (ii) high carbophilicity; and (iii) tunable electronic properties for enhancing Lewis acidity [36]. Mehdi-Zodeh and coworkers introduced cationic square planar-platinum or palladium metal complexes as Lewis acid catalysts into the Friedel-Crafts reaction between biomass-derived furans **36** and ethyl trifluoropyruvate **51**. Specifically, the use of either 2,2′-bis (diphenylphosphino)-1,1′-binaphthyl (BINAP) **62** or 9,9′-dimethyl-9,9′,10,10′-tetrahydro-9,10,9′,10′-biethenobianthracene-11,11′-bis(diphenylphosphino)-12,12′-diyl ($Me_2$-CATPHOS) **62** gave the corresponding 2-hydroxy-trifluoromethyl ethyl esters **64** in good yields with moderate to good enantioselectivities (**Figure 20**) [37].

The first enantioselective organocatalytic Friedel-Crafts reaction with biomass-derived furan **66** using the first-generation MacMillan's chiral imidazolidinone as an organocatalyst **65** was reported by the thesis of Paras in 2004 [38]. In general, the sense of high asymmetric induction using a chiral imidazolidinone catalyst for enantioselective reactions was well established with the following distinctive features—(i) *E*-selective iminium ion formation when reacting the catalyst with α,β-unsaturated aldehydes; (ii) chirality of the benzyl group on the catalyst backbone shields *re*-face of the α,β-unsaturated iminium ion, leaving the *si*-face exposed to nucleophilic addition. However, the desired Friedel-Crafts product **68** was unfortunately obtained in high yield but moderate enantioselectivity when employing biomass-derived furan **66** (**Figure 21**).

In 2010, Harada and coworker reported an organocatalytic Friedel-Crafts reaction between furans **12** and α,β-unsaturated ketones **70** using a chiral oxazaborolidinone (OXB) catalyst **69** to produce the chiral Friedel-Crafts products **71** in good to excellent yields (62–99%) with high enantioselectivities (77–93% ee) [39]. As shown in **Figure 22**, different substituted furans and α,β-unsaturated ketones were well tolerated in this reaction.

The highly enantioselective organocatalytic Friedel-Crafts reaction with biomass-derived furan **66** using chiral phosphoric acid **72** as an organocatalyst was accomplished by the Akiyama group in 2010 [40]. They utilized a highly sterically hindered phosphoric acid catalyst **72** in the Friedel-Crafts reaction of furan **66** with methyl trifluoropyruvate **73** to afford the desired product **74** in excellent yield of 99% with high enantioselectivity (82% ee) (**Figure 23**).

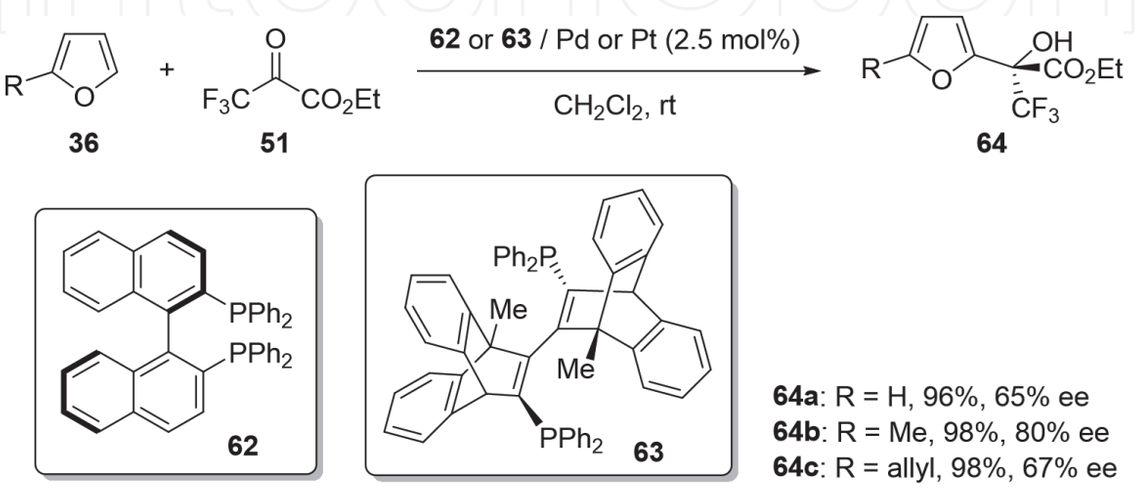


**Figure 20.**
*Enantioselective Friedel-Crafts reactions catalyzed by metal complexes catalyst.*

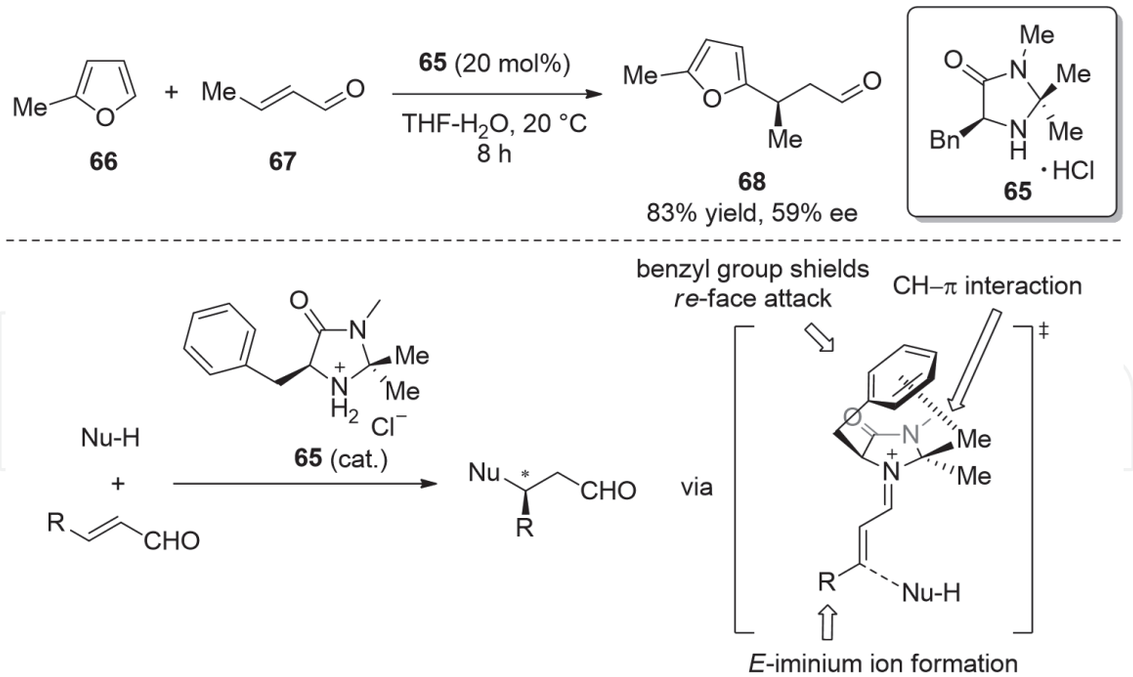


**Figure 21.**
*Enantioselective Friedel-Crafts reactions with α,β-unsaturated aldehydes.*

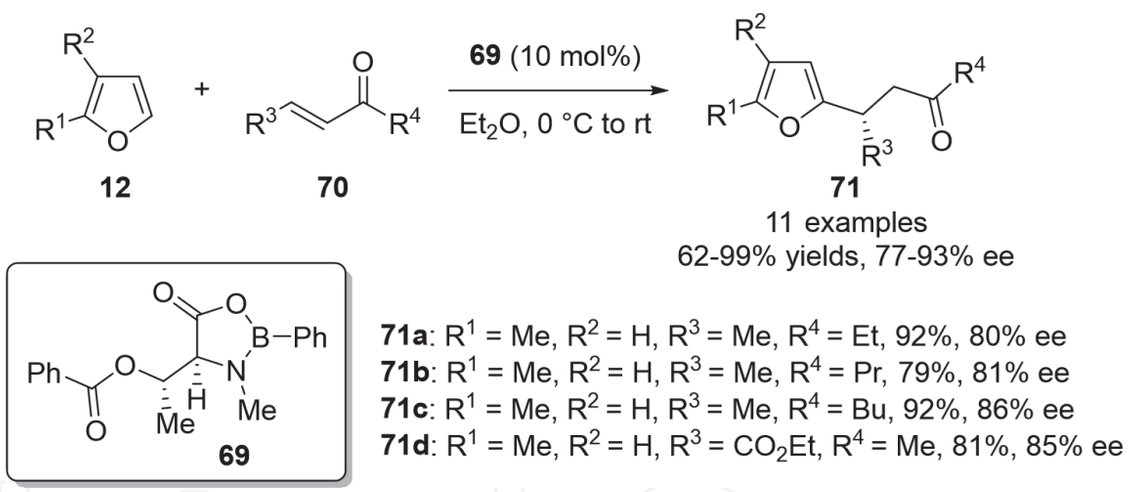


**Figure 22.**
*Enantioselective Friedel-Crafts reactions with α,β-unsaturated ketones.*

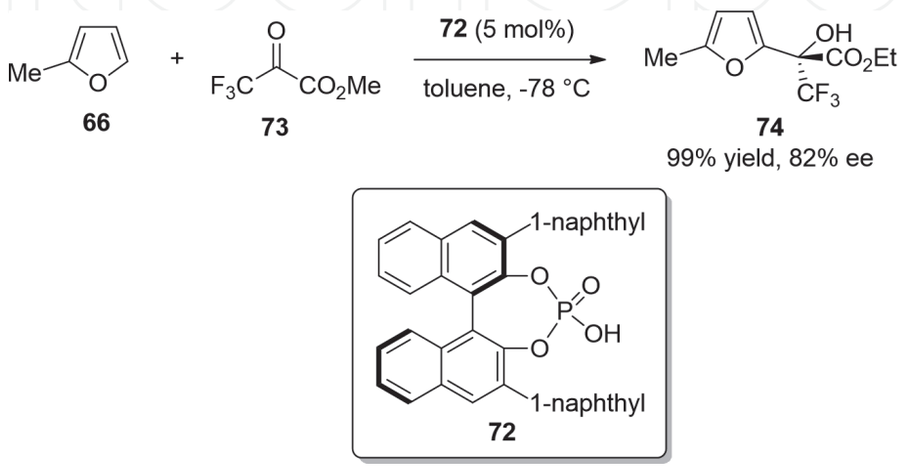


**Figure 23.**
*Enantioselective Friedel-Crafts reactions catalyzed by phosphoric acid.*

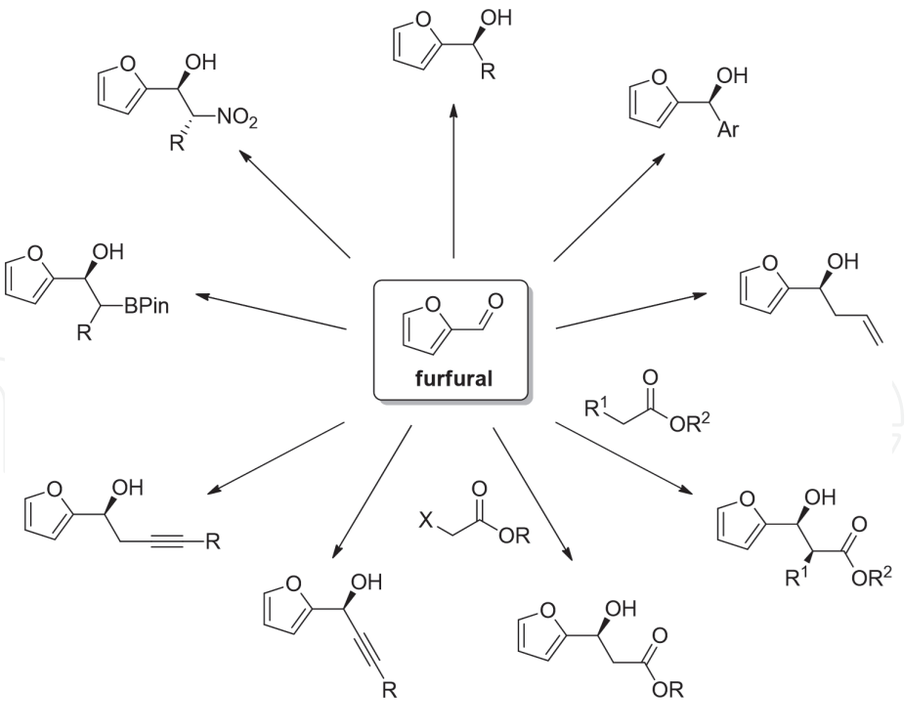


**Figure 24.**
*Various catalytic asymmetric nucleophilic addition reactions with furfural.*

## 4. Various catalytic asymmetric nucleophilic addition reactions of furfural

Asymmetric nucleophilic addition reactions with aromatic or heteroaromatic aldehyde derivatives are powerful C-C bond-forming reactions that can provide chiral hydroxy compounds with stereogenic hydroxy functional groups. Therefore, the development of asymmetric nucleophilic addition is an ongoing challenge in organic synthesis. Following the first demonstration of the catalytic asymmetric nucleophilic addition with biomass-derived furfural by the Yamamoto group in 1997 [41], numerous reports with regard to catalytic asymmetric reactions of furfural have been published including the reaction of allylation [42], aldol reactions [43, 44], nitroaldol (henry) reaction [45, 46], alkylation [47–49], acylation [50], the Reformatsky reaction [51], the Nozaki-Hiyama reaction [52], alkynylation [53], and hydroboration [54] with various types of catalysts (**Figure 24**). However, the enantioselective catalytic nucleophilic addition reaction of 5-hydroxymethylfurfural (HMF) has not yet been reported.

## 5. Conclusion

As we have shown in this book chapter, a variety of synthetic approaches, such as cycloaddition reactions, Friedel-Crafts reactions, and nucleophilic addition reactions, are elegant methodologies that have been efficiently used for the enantioselective reaction of biomass-derived furans. While Friedel-Crafts and nucleophilic addition reactions serve various furan derivatives with a chiral carbon atom in the α-position, enantioselective cyclization reactions using furans as the 4π diene component affords chiral dihydrofuran or tetrahydrofuran derivatives. Synthesizing chiral synthons or highly functionalized products derived from furan may show great potential not only for the creation of new libraries that could lead to the development of biologically active compounds but also for stimulating further

research toward versatile applications of these molecules via another asymmetric catalysis. There is no doubt that the further development of catalytic enantioselective reactions with biomass-derived furans will continue to provide exciting results in near future.





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