Organometal-catalyzed asymmetric Friedel-Crafts reactions

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The Friedel-Crafts alkylation (F-CA) reaction is a distinct sort of C–C bond formations. It is often used for the formation of C–C bonds to aromatic rings in organic synthesis. Its enantioselective version frequently provides highly enantiomer as the expected products. Generally, this asymmetric variant of asymmetric Friedel-Craft alkylation (AF-CA) proceeds via an in situ metal catalyzed generation of an enamine as an intermediate. In this report, we are trying to highlight the applications of various optically pure metal catalysts in the AF-CA as a versatile synthetic strategy in asymmetric synthesis. Metal-catalyzed AF-CA was frequently found as an important and decisive step (steps) for the effective asymmetric synthesis of complex molecules, compounds showing interesting diverse biological activities and especially in the total synthesis of naturally occurring compounds with great and various biological and pharmacological properties.

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1. Introduction

Charles Friedel, (born March 12, 1832, Strasbourg, Fr.—died April 20, 1899, Montauban), French organic chemist and mineralogist and the American chemist James Mason Crafts, (March 8, 1839—June 20, 1917) discovered in 1877 and established the chemical process known as the Friedel-Crafts Alkylation (F-CA). Initially, Crafts prepared amyl-benzene upon the treatment of amyl chloride with AlCl3 in benzene (Scheme 1) [1]. However, his achievement was not only one of the reports of the applications of a Lewis acid in organic synthesis but it was the first example of Lewis acid-catalyzed reaction for the especial kind of C–C bond formation. Nowadays, this reaction is called as Friedel-Crafts alkylation (F-CA) after its inventors; it is an important and easily operational for the alkylation of arenes and heteroarenes. There are two main types of F–C reactions. They are alkylation reactions and acylation reactions. These reactions are classified in organic chemistry as the electrophilic aromatic substitution.

The asymmetric carbon-carbon bond formation is of vibrant importance in synthetic organic chemistry. It is extensively applied for the generation of the chiral carbon (carbons) in the highly functionalized complex organic molecules, thus, widely applicable in the total synthesis of natural products with high and diverse biologically properties. Therefore, the investigations for selecting an alternative and superior approaches are in much demand. The superiority can be secured by optimizing the reaction conditions to meet the important issues and impacts such as regio-, diastereoselectivity, and enantioselectivity. Usually, these problems are avoided or solved by using of the metal- or bio-catalyzed protocols. Currently, the idea of asymmetric carbon-carbon bond-formation has been pretentiously fixated by using chiral catalysts, thus a huge number of chiral catalysts and particularly organocatalysts have been prepared and a plethora approach for asymmetric C–C bond formation have been developed [2].

As a matter of fact, the biocatalysts and organocatalysts have been long applied in contemporary organic chemistry [3]. Nevertheless, the possibility of generation of chiral centers and inductions of high levels of chirality during an organocatalyzed asymmetric reactions must be considered, carefully [4]. Nowadays, the unpredictable and casual impacts in the configurative outcomes during the formation of a C–C bond, have been largely avoided by using bio- or metal catalysts. In the past few decades, several effective biocatalysts and a huge number of metal-catalysts containing chiral ligands have been discovered and used in diverse chemical transformations permitting the developments of many protocols for efficient asymmetric synthesis. These approaches can be successfully applied in the art of total synthesis of natural products which nowadays are attracted much attention of synthetic organic chemists. Their interests have led to the discovery of several catalysts and developments of a plethora of approach, revealing its overgrowing impact.

In continuation of our interest in asymmetric synthesis [13], and due to the importance of metal catalyzed-F-CA reactions, we were encouraged and thought it was worthwhile to underscore applications of metal catalyzed AF-CA reactions. Therefore, in this review, we try to outline the recent developments in metal catalyzed AF-CA reactions. This review covers the progress associated with the synthesis of extremely functionalized enantiomerically enriched molecules via AF-CA transformation using various metal catalysts. In this review, we try to underscore the recent advances on organometal catalyzed -F-CA by using organometals such as Pd, Au, In, Ir etc.

2. Organometal catalyzed asymmetric Friedel-Crafts reactions using

2.1. Palladium

The catalytic AF-C-type alkylation reaction improved by utilization chiral Pd complexes [14] is demonstrated in 2011. The reaction between indoles and γ,δ-unsaturated β-ketophosphonates in the mild reaction conditions provided the desired AF-CA products with high ee (up to 99%) [15].

Based on the optimal conditions, the enantioselective AF-CA of different indoles 4 and γ,δ-unsaturated β-ketophosphonates 3 afforded the desired alkylated adducts 6a-n in excellent yields and ee (85–99%). The greatest enantioselectivity of F–C products 6d and 6k has been provided in toluene, and F–C products 6i, 6j and 6l has been produced in dichloromethane. Instead, dimethyl 2-oxo-4-phenyl-but-3-enylphosphonate 3e and indole 4a under the optimized reaction conditions could not be alkylated (Scheme 2, Table 1).

Additionally, indole derivatives 4 have been also employed as precursors in this AF-CA reaction with dimethyl 2-oxo-pent-3-enylphosphonate 3a. It was known that the desired adducts 8 have been provided in excellent yields and ee value (Scheme 3) [15]. The chiral dicaticonic palladium complexes, containing sterically demanding diphosphine ligands as Lewis acid catalysts mediated the stereoselective F–C-type alkylation reaction of pyrroles and indoles with γ,δ-unsaturated z-ketoesters, to give the AF-CA adducts having benzylic stereocenters in excellent ee and chemical yields. The F–C adducts can be easily functionalized to offer z-hydroxy esters through catalytic stereoselective ene sequences [16].

Next, the F–C product was converted into z-hydroxy esters with a quaternary stereocenter through a sequential catalytic carboxyli-

![Scheme 1. AlCl₃-catalyzed reaction of amyl chloride and benzene developed by Friedel and Crafts.](image-url)
ene reaction (Scheme 4) [17]. Using Pd(PPH₃)₂(SbF₆)₂ system, the ene reaction of racemic F-C product 9a and acetone silyl enol ether 10 provided the desired product 12a comprising both tertiary and quaternary stereocenters in excellent yield however in poor syn-selectivity (Scheme 4, Eq. 1: anti/syn 43/57). The mixture of 9a and 10 using (R)-SEGPHOS-Pd system 11 (5 mol %) resulted in the ene product 12a with a high anti-selectivity (Eq. 2: anti/syn 92/8). On the other hand, the reaction mediated by ent-11 containing (S)-SEGPHOS gave the corresponding product 12a in an excellent yield, but, the de very reduced (Eq. 3: anti/syn 54/46). Whereas the application of 11 and 9b afforded the ene product 12b in excellent yield and de (Eq. 4: anti/syn 97/3). Significantly, ent-11 resulted in the poor de (Eq. 5: anti/syn 40/60).

Then, the catalytic stereoselective AF-CA of N-methyl pyrrole 7 and different β,γ-unsaturated α-ketoesters 13 using complex 14 have been tested. Once the treatment of 7 and 13a was performed in CH₂Cl₂, the almost enantiopure adduct 15a was provided in a 95% chemical yield. Moreover, an excellent ee and yield might be preserved even on 1 mol % of catalyst loading (98% ee and 94% yield) but 0.5 mol % of catalyst loading reduced both ee and yield (89% ee and 85% yield). α-Ketoesters 13b-e having electron-donating and –withdrawing aromatic substituents and also aliphatic substituents on activated alkene portion have been surveyed to afford the corresponding adducts in high ee, although the dialkylated adduct has been produced by reaction of 13e in a 17% chemical yield. The application of 13f with dienyl substituent provided the expected 1,4-addition compound 15f in excellent yield and ee value and without the 1,6-addition compound (92% yield and 95% ee). Phthaloyl substituent of 13g had no deteriorating influence on the yield but reduced the ee (97% yield and 84% ee) (Scheme 5, Table 2) [16].

The catalytic AF-CA reaction using chiral Pd systems [14c,15,18] was demonstrated in Scheme 6. The reaction of indole derivatives and fumarates gave the desired F-CA products with excellent ees. The AF-C reaction of different indole derivatives 4 and fumarates 16 afforded the relevant alkylated compounds 18 in moderate to excellent yields and up to 91% ees (Table 3) [19].

However, the reason for the obtained enantioselectivity is still uncertain. However, it can be that fumarates 16 were promoted by the Pd catalyst 17 via bidentate approach. In the following, indole attacks the double bond. Since the Si face of the double bond of phosphonate has been obstructed specially with one of the phenyl substituents of (R)-BINAP, the addition of indole advanced from the Re face in an extremely asymmetric method (Fig. 1) [19].
An efficient catalytic stereoselective synthetic protocol for providing compounds containing an all-carbon quaternary spiro center has been reported relied on the palladium-mediated intramolecular ipso-FC allylic alkylation of phenols. Once utilizing 6 mol % of the Trost ligand (R,R)-21 [20], the spirocyclic products have been generated in moderate yields and with up to 89% enantioslectivity (de = 9.2:1) (Scheme 7) [21].

The related argument is reinforced using the experimental outcomes displayed in Scheme 8. Once a phenol derivative containing a chloride substituent on the meta-position to the phenol has been used as the substrate, the ee reduced extremely in comparison with that provided once applying 23 as the substrate. This outcome may be rationally clarified by the variance in the van der Waals radius between the Me and the Cl substituents.

In the following, utilizing Pd(dba)2, (R,R)-21, and lithium carbonate at ambient temperature, the spirocyclization of 27 was successful.

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In the following, utilizing Pd(dba)2, (R,R)-21, and lithium carbonate at ambient temperature, the spirocyclization of 27 was successful.
achieved and afforded the related product 28 in measureable yield and with 77% enantioselectivity ($de = 1.9:1$, minor diastereomer: 69% ee). Moreover, the spirocyclization reaction of 29 gave the related spirocyclic product 30 in high yield. However, the $de$ of this reaction was 1:1 (Scheme 9) [21].

The extremely AF-C-type alkylation of furan and thiophenes with trifluoropyruvate that have never afforded the excellent value of stereoselective induction and yield until now, has been accomplished by employing dicationic Pd systems as Lewis acid catalysts. Dicationic palladium-catalyst 33 was synthesized spontaneously from the related dichloride system and two equivalents of silver hexafluoroantimonate (V) [17b,22].

Furthermore, glyoxylate in place of trifluoropyruvate as an electrophile provide whole modification of regioselectivity with 2-trimethylsilylated furan, thiophene, and pyrroles to offer the expected heteroarylated compounds in excellent yields and ee. Under the optimal conditions, non-substituted furan showed high yields (95% and 99% ee), while it was rigid to achieve both excellent enantioselectivity and yield as in the preceding reports [23]. Furans 31 containing aromatic and aliphatic groups at the 5-position similarly afforded the respectable consequences. Furan having a phenyl group at the 3,5-positions could be applied regardless of steric hindrance (82% and 99% ee). The treatment of furan having an electron-withdrawing ester substituent did not accomplish even through the reflux conditions. Non- or Me-substituted thiophenes were agreeable to the extremely AF-C-type alkylation transformation (Scheme 10) [24].

The generality of the substrates was examined in catalytic stereoselective AF-CA transformations of 2-trimethylsilylated heteroaromatics and ethyl glyoxylate 36. All compounds produced the desired products 38 attached onto the trimethylsilylated carbon having excellent ee. Mono-substituted furan 35a and 2,5-disubstituted derivatives 35b-d gave with great to excellent ee value (94–99%). The treatment of 2,3,5-trisubstituted furans 35e afforded the corresponding product in excellent yield, but the ee diminished with a deleterious influence on the steric hindrance (95% and 82% ee). 2,4,5-Trisubstituted furans 35f assisted the transformations to afford high outcomes (89% and 99% ee). Furthermore, the treatment with mono- and disubstituted thiophenes 35g-j provided excellent chemical yields (85–93%) and ee (98–99%) (Scheme 11).

In sharp contrast to a heteroaromatic complex, the mixture of vinylsilane 39 and ethyl trifluoropyruvate 32 afforded the alkenylated compound 40 in 92% yields and with 98% enantioselectivity upon desilylation. These high yield and excellent ee can be attributed to the smaller steric repulsion of 39 and the trifluoromethyl substituent compared to that of 35a (Scheme 12, Eq. 1). In addition,
dienylsilane 41 afforded the dienylated compound 42 in 82% and with 99% enantioselectivity under the same reaction conditions (Scheme 12, Eq. 2).

Next, the Pd-mediated approach was examined for a two-directional reaction. The F-CA of furan 35a and trifluoropyruvate 32 in the presence of 37 (2 mol %) based on the optimal reaction conditions, gave intermediate 43a which upon treatment with glyoxylate 36 resulted in the two-directional product 44 in 91% yield with 99% enantioselectivity as a single diastereomer without the detection of the undesired meso type product (Scheme 13).

Moreover, it was endeavored to convert alkynyldiols to α-hydroxy esters via a one-pot method. Alkynyldiol 45 which can be easily provided from its corresponding α-hydroxy ketone, in toluene has been transformed spontaneously to 2-trimethylsilylated furan 47f via intramolecular cyclization in the presence of cationic gold catalyst 46a [25]. Ethyl glyoxylate 36 and dicationic Pd catalyst 37 were dissolved in CH2Cl2 and then was transferred to a solution of 45, the F–C type reaction was proceeded to provide the heteroarylated compound 48 in 57% yield and with 99% enantioselectivity (Scheme 14, Eq. 1). In a similar approach the glyoxylate system, upon intramolecular cyclization of alkynyldiol 49 in the presence of gold catalyst 46b followed by F–C reaction with trifluoropyruvate 32 resulted in the formation of compound 51 in 62% chemical yield and with 99% enantioselectivity (Scheme 14, Eq. 2) [24].

The Pd-mediated stereoselective allylic alkylation of indoles and 1,3-diphenyl-2-propenyl acetate employing P/N-kind ligands like N-aryl indole, carbon-nitrogen bond axially chiral aminophosphine (aS)-53 [26], generated the corresponding products 54 in moderate yields and good to excellent ee (up to 90%) [27]. With the optimum conditions in hand, the Pd-mediated stereoselective allylic alkylation of diverse indoles and 1,3-diphenyl-2-propenyl acetate employing N-aryl indole carbon-nitrogen bond axially chiral aminophosphine (aS)-53 was examined. The transformations with Me-substituted indoles, excepting for N-methylindole, generated the desired compounds in satisfactory ee value but with moderate yields. Instead, the transformation employing N-methylindole did not afford the desired compound. Once, 6-MeO-indole was applied, the reaction afforded the expected product 54g with satisfactory ee. Although, the treatment of 6-benzyloxyindole and 5-methoxyindole provided the corresponding product with satisfactory ee. The treatment with halogen-substituted indoles afforded the expected products with moderate to excellent ee. Applying 6-Br-indole afforded the corresponding adduct 54j moderate yield and high ee (90%). When, the treatment of 6-bromoindole has been happen in trifluoromethyl benzene in place of toluene, the ee value of 54j has been reduced to 86% enantioselectivity. In addition, the treatment of 6-Cl-indole provided the desired adduct 54l in excellent ee (86%). Instead, reaction utilizing 6-NO2-indole did not accomplish through these conditions. Lastly, the treatment of 2-phenylindole in toluene and trifluoromethyl benzene was examined. The transformations produced the desired product 54n with 86% yield and 88% enantioselectivity, respectively (Scheme 15, Table 4) [27].
Based on mild reaction conditions, Pd-mediated enantioselective intramolecular F–C type allylic alkylation of phenols has been achieved. By using Pd2(dba)3 with (1R,2R)-DACH-phenyl Trost ligand (56) [28] at 50 °C in toluene, the reaction afforded different C4 functionalized tetrahydroisoquinoline derivatives with good to high yields, regioselectivity and enantioselectivity. [29] To survey the generality of the reaction, different substrates have been examined under the optimal conditions. Commonly, all substrates having various groups on the aromatic ring and benzyl substituent on the linked nitrogen atom provided the F-CA products in good to high yields. Regioselectivity preferring the ortho alkylated product has been produced in 83% yield with 2.6/1 regioselectivity. For the substrate containing 6-methoxy substituent, the allylic alkylation product has been produced in 86% yield with 2.6/1 regioselectivity. Noticeably, once a group was entered at the 2-position of the phenol, the allylic alkylation reaction gave a single regioisomer with high enantioselectivity. For the substrate containing 6-methoxy substituent, the allylic alkylation product has been produced in 86% yield with 2.6/1 regioselectivity. Noticeably, once a group was entered at the 2-position of the phenol, the allylic alkylation reaction gave a single regioisomer with high enantioselectivity. Once an electron-donating group has been introduced on the aromatic ring, a single isomer of the C-type allylic alkylation product has been produced in 83% yield with 2.6/1 regioselectivity preferring the ortho alkylated product. 57. Using a strong electron-withdrawing substituent such as 6-N02, a noticeable reduced yield has been provided but with high enantioselectivity. Noticeably, once a group was entered at the 2-position of the phenol, the allylic alkylation reaction gave a single regioisomer by alkylation at the para-position but with a sharply reduced enantioselectivity. Fascinatingly, masking substituents for instance allyl and methyl on the linked nitrogen atom could give alkylation products in high enantioselectivity (Scheme 16, Table 5) [29].

Various indole-based peri-annulated compounds have been formed through transition-metal-mediated allylic alkylation reaction. Using Pd catalyst [30], indole-based nine-membered ring compounds have been provided in 40–70% chemical yields. Using iridium as catalyst [31], extremely enantioenriched seven-membered ring products have been provided in 40–78% chemical yields and 91–97% enantioselectivity. Once 3-functionalized indole substrates have been used with a Pd catalyst, enantioselective allylic dearomatization of indole derivatives occurred with products provided in 48–78% yields and 35–78% enantioselectivity with a chiral ferrocene-based PHOX ligand. Fascinatingly, using an Ir catalyst, F–C-type allylic alkylation at the C5 position of indole gave the corresponding products in 40–60% chemical yields and 56–97% enantioselectivity [32]. Also, reaction of 7-functionalized indole derivatives produced the desired products in moderate yields. 2-Functionalized indole derivatives having both substituents could be applied in the reaction. In addition, aliphatic substituents provided the corresponding products in good yields (Scheme 17, Table 6) [32].

2.2. Iridium

You and co-workers demonstrated the diverse construction of indole-based peri-annulated compounds through transition-metal-mediated allylic alkylation. From the 4-indolyl allylic

---

**Table 4**

| Entry | R     | Yield (%) | ee (%) |
|-------|-------|-----------|--------|
| 1     | H     | 89 (54a)  | 80     |
| 2     | 4-Me  | 93 (54b)  | 33     |
| 3     | 5-Me  | 85 (54c)  | 36     |
| 4     | 6-Me  | 76 (54d)  | 33     |
| 5     | 7-Me  | 65 (54e)  | 37     |
| 6     | N–Me  | n.r.      | —      |
| 7     | 5-MeO | 85 (54f)  | 40     |
| 8     | 6-MeO | 69 (54g)  | 75     |
| 9     | 6-BnO | 69 (54h)  | 34     |
| 10    | 5-Br  | 88 (54i)  | 58     |
| 11    | 6-Br  | 80 (54j)  | 90     |
| 12    | 6-Br  | 74 (54k)  | 86     |
| 13    | 5-Cl  | 73 (54l)  | 80     |
| 14    | 6-Cl  | 77 (54m)  | 86     |
| 15    | 6-F   | 83 (54n)  | 84     |
| 16    | 6-NO2 | n.r.      | —      |
| 17    | 2-Ph  | 81 (54o)  | 86     |
| 18    | 2-Ph  | 88 (54n)  | 88     |

**Scheme 15.** Palladium-mediated asymmetric allylic alkylation of indoles and 1,3-diphenyl-2-propenyl acetate using (αS)-53.

**Scheme 16.** Pd-mediated enantioselective intramolecular F–C type allylic alkylation reaction of phenols.

**Table 5**

| Entry | R     | Yield (%) | ee (%) |
|-------|-------|-----------|--------|
| 1     | H     | 73 (57a)  | 92     |
| 2     | 6-MeO | 83 (57b)  | 85/15  |
| 3     | 4-Br  | 80 (57c)  | 90     |
| 4     | 4-Br  | 61 (57d)  | 91     |
| 5     | 6-O2N | 30 (57e)  | 92     |
| 6     | 5-HO  | 93 (57f)  | 66     |
| 7     | 5-HO  | 86 (57g)  | 72     |
| 8     | 2-MeO | 73 (57h)  | 20     |
| 9     | 2-Cl  | 61 (57i)  | 3      |
| 10    | H     | 75 (57j)  | 91     |
| 11    | 4-Br  | 38 (57k)  | 92     |
| 12    | H     | 71 (57l)  | 99     |
| 13    | 6-MeO | 91 (57m)  | 84     |
| 14    | 4-Br  | 43 (57n)  | 90     |
| 15    | H     | 50 (57o)  | 38     |
carbonates, using Ir or Pd complexes, four kinds of alkylation compounds changing the reaction position of indole and ring size might be provided (Scheme 18) [32].

The generality of this reaction has been examined under the optimal reaction condition involving [Ir(cod)Cl]2. 66, caesium carbonate in dichloromethane under reflux condition. Both allyl and benzyl substituents provided alkylated compounds in high enantioselectivity. Reaction of 7-functionalized indoles produced the aliphatic substituent functionalized indoles provided excellent enantioselectivity, however in good yields (Scheme 19, Table 7) [32].

Also, Substrates containing allyl, methyl, and benzyl substituent at the 3-position of indole were applied in the reaction. Using 3-benzyl indole, the corresponding products have been provided with moderate yields and enantioselectivity. Besides, substrates bearing an aryl substituent at the 3-position of indole were appropriate in this reaction. Changing the electronic and substituent pattern on the benzyl substituent at the C3 position of indole presented no remarkable influence on the reaction result, and the corresponding products have been provided with moderate yields and good enantioselectivity (Scheme 20) [32].

An Ir-mediated [33] intramolecular F–C type allylic alkylation reaction of phenols 66 afforded tetrahydroisoquinoline derivatives 70 and 71 with good to high yields, ee, and moderate regioselectivity. Both allyl and benzyl substituents on the linked nitrogen atom provided alkylated products in high enantioselectivity. Substrates containing both electron-withdrawing and donating substituents at the 2-, 4-, or 6-position of phenol have been examined in this reaction. Using phenols having a group at the 2-position, the aliphatic alkylation gave a single regioisomer through reacting at the para-position of the phenols. Also, once a group has been endured at the 4 or 5 position of the phenol ring, a single isomer has been provided with moderate to high yields and enantioselectivity. Using 3-aryl substituent at the 3-position of indole were applied in this reaction. Using 2-aryl indole, the corresponding products have been provided with moderate yields and excellent enantioselectivity. Besides, substrates bearing an aryl substituent at the 2-position of indole were applied in the reaction. Using 2-aryl indole, the corresponding products have been provided with moderate yields and enantioselectivity. Using 2-aryl indole, the corresponding products have been provided with moderate yields and enantioselectivity. Using 2-aryl indole, the corresponding products have been provided with moderate yields and enantioselectivity.

A proposed diversity oriented formation of indole-based peri-annulated compounds.

### Table 6

| Entry | X, R1, R2 | Yield (%) |
|-------|-----------|-----------|
| 1     | n-Bn, H, H | 70 (61a)  |
| 2     | N-allyl, H, H | 40 (61b)  |
| 3     | n-Bn, Me, H | 68 (61c)  |
| 4     | n-Bn, F, H | 57 (61d)  |
| 5     | n-Bn, Cl, H | 60 (61e)  |
| 6     | n-Bn, H, Ph | 64 (61f)  |
| 7     | n-Bn, H, 4-MeC6H4 | 68 (61g)  |
| 8     | n-Bn, H, 4-ClC6H4 | 68 (61h)  |
| 9     | n-Bn, H, Me | 40 (61i)  |
| 10    | n-Bn, H, allyl | 50 (61j)  |
| 11    | C(CO2Me)3, H, H | 70 (61k)  |

### Table 7

| Entry | X, R1, R2 | Yield (%) | ee (%) |
|-------|-----------|-----------|--------|
| 1     | n-Bn, H, H | 2/98     | 60 (63a) 94 |
| 2     | N-allyl, H, H | 1/99     | 51 (63b) 94 |
| 3     | n-Bn, Me, H | 1/99     | 46 (63c) 94 |
| 4     | n-Bn, F, H | 4/96     | 64 (63d) 93 |
| 5     | n-Bn, Cl, H | 6/94     | 62 (63e) 93 |
| 6     | n-Bn, H, Ph | 2/98     | 78 (63f) 94 |
| 7     | n-Bn, H, 4-MeC6H4 | 1/99     | 76 (63g) 91 |
| 8     | n-Bn, H, 4-ClC6H4 | 2/98     | 68 (63h) 91 |
| 9     | n-Bn, H, Me | 1/99     | 40 (63i) 95 |
| 10    | n-Bn, H, allyl | 1/99     | 60 (63j) 97 |

![Scheme 17](image1.png)

Substrate scope for Pd-catalyzed F–C type allylic alkylation of indole fused.

![Scheme 18](image2.png)

Proposed diversity oriented formation of indole-based peri-annulated compounds.

![Scheme 19](image3.png)

Substrate scope for Ir-catalyzed AF–C type allylic alkylation reaction of indole fused.

![Scheme 20](image4.png)

Substrate scope for Pd-catalyzed AF–C type allylic alkylation reaction of indole fused.
gave the best enantioselectivity [35]. This method features high chemoselectivity and ee, and a readily accessed chiral ligand [36], based on this method, N- benzyl, methyl, and allyl substituents provided alkylated products 74a-c in high enantioselectivity (98->99%). The reactions of 5-functionalized indole substrates produced the corresponding products 74d-h in moderate yields 70–77% and high enantioselectivity (98->99%). Substrates containing both an electron-donating substituent (methoxy) and an electron-withdrawing substituent (Cl) at the 6-position of indole provided the relevant products in moderate yields with high enantioselectivity (Scheme 22) [37].
(M = Rh, Ir) [38] mediated the alkylation of heteroaromatics and α,β-unsaturated aldehydes having aromatics nevertheless in some cases, combinations of adducts have been provided. Furthermore, complexes 83 and 78 have been applied to stimulate nitroalkenes for the AF-CA reaction of a variety of aromatics and heteroaromatics, especially, 1,3,5-trimethoxybenzene. For this compound, the monoalkylated product has been produced in quantitative chemical yield with ee’s of up to 73% enantioselectivity being accomplished [39]. CH2Cl2 was utilized as solvent and reactions have been accomplished at under 4 Å molecular sieves (MS). A 1:20:60, catalyst/aromatic/enal molar ratio was used. Although, the Ir complex 78 mediated the treatment of m-N,N-dimethyl anisidine 76 and trans-crotonaldehyde 77. Upon 72 h of reaction, the monosubstituted F–C adduct at the para-position with respect to the amine has been provided in 26% ee and 49% chemical yield, measured on the alcohol provided by reduction with sodium borohydride. Analogously, complex 78 mediated the treatment of anisidine 76 and methacrolein, but a mixture of three products has been produced. Upon reduction with sodium borohydride, the main adduct was identified as alcohol 80b. The NMR data demonstrated that the two remaining adducts were the other two probable monosubstituted F–C products 80c and 80d (Scheme 23) [39].

Then, the AF-CA of indoles and enals was tested. N-methyl pyrrole 7b treated with trans-crotonaldehyde 82 to afford the desired 2-substituted F–C product 84, with 8% or 12% enantioselectivity when the Rh complex 83 or the Ir complex 78 have been applied as the catalyst precursor, respectively. No transformation was occurred upon the reaction of N-benzyl pyrrole 7b and enals 81, 82 in the presence of complexes 83 or 78 (Scheme 24) [39].

In the continuation, the treatment of a number of indoles having trans-crotonaldehyde and methacrolein using Ir complex 78 as a catalyst precursor has been surveyed. The indole has been alkylated at the 3-position in all the situations surveyed. The chemical yields of the obtained alcohol from the reduction of the F–C adduct, were found being 15–58%. Enantiomeric excesses from 7 to 33% have been accomplished (Scheme 25) [39].

Besides, it was examined the treatment of trans-β-nitrostyrene as an alkene model, having a wide range of activated arene derivatives 87a–c, N-methyl pyrrole 7a and indole utilizing the Ir complex 78 as a catalyst precursor. CH2Cl2 was applied as solvent and reactions have been happen, under 4 Å MS. Only monosubstituted F–C products have been identified, the arene substituted at the para-position with regard to amine 88a, for m-N,N-dimethyl anisidine 87a and 3-substituted indole 88e or 2-substituted pyrrol 88d for the heteroaromatic compounds. Enantiomeric excesses changing from 3% to 40% enantioselectivity have been observed (Scheme 26) [39].

Subsequently, the best consequences have been provided for 1,3,5-trimethoxybenzene 90 (quantitative chemical yield upon 6 h of reaction, 40% enantioselectivity). The reaction of compound 90 and a wide range of trans-β-nitrostyrenes was examined. Scheme 27 and Table 9 demonstrate the results provided from the

\[
\text{Scheme 23. Catalytic reaction of } m\text{-N,N-dimethylanisidine and trans-crotonaldehyde.}
\]

\[
\text{Scheme 24. Catalytic reaction of pyrroles and enals.}
\]

\[
\text{Scheme 25. Catalytic reaction of indoles and enals.}
\]

\[
\text{Scheme 26. Reaction of several aromatics and heteroaromatics with trans-β-nitrostyrene.}
\]
catalytic transformation of unsubstituted trans-β-nitrostyrene in the presence of complex 78 as a catalyst, under the aforementioned reaction conditions [39].

An AF-CA of 2-nitro-3-arylacrylates and indoles, mediated by a metal-templated hydrogen bonding catalyst was reported by Gong and co-workers [40]. The stereoselective induction relies on chirality transfer only from the octahedral metal stereocenter through three weak hydrogen bonds. All the corresponding products were produced with moderate to high ee whereas modest de that can be transformed into a number of useful indole-having chiral building blocks involving tryptophans [40]. In the following, it was examined the substrate generality of the AF-CA of (Z)-2-nitro-3-arylacrylates and indoles. The (Z)-ethyl 2-nitro-3-phenylacrylate produced the corresponding adduct 94c in 96% yield and excellent ee of 94% and 92% ee for the two diastereomers.

Although diastereoselectivities stay poor for all explored reactions, yields and ee are normally excellent. The (Z)-2-nitro-3-arylacrylates endure methyl substituents 94a,b and electron withdrawing functional substituents 94d-g in the phenyl framework, the ethyl ester can be exchanged by a methyl 94h and isopropyl 94i ester, although the phenyl substituent can be switched by a naphthyl scaffold 94j. Moreover, indole derivatives are endured 94k-n, while the methylation of the NH-group resulted in a substantial decline in ee of both diastereomers (12%/39% ee) and is due to a hydrogen bond of the indole NH group and the carboxamide scaffold of the catalyst is a requisite for attaining excellent ee value (Scheme 28, Fig. 2) [40].

The F-CA reaction of 3,3,3-trifluoropyruvates and indole derivatives was mediated by the Ir system [(η5-C5Me5)Ir[(R)-Prophos] (H2O)][SbF6]2 96 with up to 84% enantioselectivity [41]. Remarkably, experimental and theoretical data assisted to suggest a Table 9
Reactions of 1,3,5-trimethoxybenzene and trans-β-nitrostyrenes.

| Entry | R       | t (h) | Yield (%) | ee (%) |
|-------|---------|-------|-----------|--------|
| 1     | H (89c) | 6     | >99 (91c) | 40     |
| 2     | 4-Me (89f) | 14   | >99 (91f) | 54     |
| 3     | 2-MeO (89g) | 16   | 94 (91g) | 73     |
| 4     | 3-MeO (89h) | 7    | >99 (91h) | 18     |
| 5     | 4-MeO (89i) | 15   | >99 (91i) | 51     |
| 6     | 2-BnO (89j) | 17   | 69 (91j) | 69     |
| 7     | 3-BnO (89k) | 21   | 83 (91k) | 15     |
| 8     | 4-BnO (89l) | 17   | 98 (91l) | 43     |
| 9     | 2,3-(Me)2O (89m) | 24  | 89 (91m) | 70     |
| 10    | 2,4-(Me)2O (89n) | 22  | 22 (91n) | 51     |
| 11    | 2,5-(Me)2O (89o) | 24  | 95 (91o) | 40     |
| 12    | 3,4-(Me)2O (89p) | 22  | 92 (91p) | 67     |
| 13    | 3,4-(Bn)2O (89q) | 25  | 96 (91q) | 20     |
| 14    | 3,5-(Bn)2O (89r) | 18  | >99 (91r) | 9      |
| 15    | 3-BnO/4-MeO (89s) | 18  | 97 (91s) | 35     |
| 16    | 2-F (89t) | 4    | >99 (91t) | 22     |
| 17    | 2-Cl (89u) | 22  | 92 (91u) | 31     |
| 18    | 2-Br (89v) | 25  | 89 (91v) | 21     |
| 19    | 4-CI (89w) | 22  | >99 (91w) | 9      |
| 20    | 4-Br (89x) | 16  | >99 (91x) | 9      |
| 21    | 2,3-(Cl)2 (89y) | 40  | 95 (91y) | 0      |
| 22    | 2,4-(Cl)2 (89z) | 17  | 60 (91z) | 0      |
| 23    | 2,6-(Cl)2 (89ab) | 49  | 2.5 (91ab) | 3     |
| 24    | 2-Cl-6-F (89ac) | 118 | 50 (91ac) | 47     |
| 25    | 2-F-6-C (89ad) | 96  | 22 (91ad) | 9      |

Scheme 27. Reactions of 1,3,5-trimethoxybenzene and trans-β-nitrostyrenes.

Scheme 28. A stereoselective AF-CA transformation of 2-nitro-3-arylacrylates and indoles mediated by a metal-templated hydrogen bonding catalyst.
asymmetric 2-alkylation of 3-functionalized indole derivatives chiral Lewis acid/hydrogen bond-catalyzed permits the challenging activation through hydrogen bond production. This bifunctional trophile activation through metal coordination with nucleophile normally at /C0 derivatives has been achieved in a substoichiometric method.

\[ \text{Table 10} \]

**AF-C hydroxyalkylation reactions of indoles and pyruvates.**

| Entry | Cat. | R1 | R2, R3, R4 | Yield (%) | ee (%) |
|-------|------|----|------------|-----------|--------|
| 1     | Et   | H, H, H | >99 (97a) | 65        |
| 2     | Et   | Me, H, H | >99 (97b) | 47        |
| 3     | Et   | Me, H, H | >99 (97c) | 76        |
| 4     | Et   | Me, Me, H | 96 (97d) | 52        |
| 5     | Et   | H, 5-MeO | >99 (97e) | 71        |
| 6     | Et   | H, 5-Cl | 96 (97f) | 76        |
| 7     | Et   | H, Me, 5-MeO | 97 (97g) | 55        |
| 8     | Et   | H, Me, 5-Cl | >99 (97h) | 80        |
| 9     | Me   | H, H | >99 (97i) | 68        |
| 10    | Me   | Me, H, H | 98 (97j) | 50        |
| 11    | Me   | H, H, H | 99 (97k) | 71        |
| 12    | Me   | H, 5-Cl | 95 (97l) | 80        |
| 13    | Me   | Me, 5-Cl | 99 (97m) | 84        |
| 14    | Et   | H, Me, 5-Cl | 99 (97n) | 73        |
| 15    | Et   | H, 5-Cl | 99 (97o) | 72        |
| 16    | Et   | H, H | 99 (97p) | 69        |
| 17    | Et   | H, Me, 5-Cl | 98 (97q) | 71        |
| 18    | Me   | H, H | >99 (97r) | 73        |
| 19    | Me   | Me, 5-Cl | 99 (97s) | 82        |
| 20    | Et   | H, H, 5-Cl | 92 (97t) | 8        |
| 21    | Et   | H, Me, 5-Cl | 99 (97u) | 34        |

Fig. 2. Proposed transition state of the AF-CA catalyzed by \( \alpha \)-Ir.

Scheme 29. AF-C hydroxyalkylation reactions of indoles and pyruvates.

2 mol %. As an application, the straightforward synthesis of a chiral pyrrolo-[1,2-\( \alpha \)]indole is shown in Scheme 30 [44]. Various \( \alpha,\beta \)-unsaturated 2-acyl imidazole derivatives, by using 2 mol % of \( \alpha,\beta \)-Ir99 in toluene provide \( \alpha,\beta \)-unsaturated 2-acyl imidazole derivatives bearing diverse groups at the imidazole nitrogen (products \( 100b \) and \( 100c \)), functionalized aromatic scaffolds (products \( 100d - j \)), a thiophene (product \( 100k \)), or a methyl substituent (product \( 100l \)) at the \( \beta \)-position in yields of 55–99% yield and 92–98% enantioselectivity [44].

A highly active catalyst for the AF-CA of indole derivatives and \( \beta,\beta \)-disubstituted nitroalkene derivatives was described. Bis-cyclometalated \( \text{Ir(III)} \) system as catalyst was used as low as 0.05 mol% for this AF-CA reaction of indoles, giving valuable synthetic frameworks having an all-carbon quaternary stereocenter. The bis-cyclometalated \( \text{Ir(III)} \) system [45] as a structural pattern and through the ligand sphere makes hydrogen bonding with the two substrates. By preceding plan, the catalyst was rendered \( \text{C}_2 \)-symmetrical to increase the atom economy of this catalyst moiety (two catalytic centers per \( \text{Ir} \) system). More significantly, this rational design limits the conformational freedom of a key hydrogen bond acceptor, being responsible for the promotion of the indole nucleophile and bringing it in a perfect situation for the proposed ternary transition state (Fig. 3) [46].

By using 0.1 mol% of catalyst \( \text{A-}(R,R)-\text{Ir101} \) at 20 °C, various 1-aryl-2-nitroacrylates including different ester substituents (products \( 103a, b \), electron-donating (products \( 103c-e \)) or electron-withdrawing groups (products \( 103f, g \)) in the phenyl scaffold and one heteroaromatic scaffold (product \( 103h \)) gave the all-carbon quaternary carbon products \( 103a-h \) in excellent yields and high ees. This is consistent with the suggested mechanism in which a hydrogen bond between the indole nitrogen-hydrogen and the carbamoyl scaffold of the catalyst was required for affording an electronic activation and providing excellent enantioselective induction (Scheme 31) [46].

2.3. Copper

An extremely AF-CA of pyrrole and \( \beta,\gamma \)-unsaturated \( \alpha \)-ketoester derivatives has been achieved using a chiral Cu system [47], to give the alkyated derivatives of pyrrole with high ees and moderate yields [48]. Based on the optimal reaction condition, the substrate generality of \( \beta,\gamma \)-unsaturated \( \alpha \)-ketoester derivatives for the F-CA has been examined. First, the electronic influence has been tested.
by changing the \( R^1 \) groups of \( R^1 \). The electron-donating substituents provided moderate yields and high enantioselectivity. On the other hand, for the electron-withdrawing substituents, for instance \( F \), \( Cl \), and \( Br \) substituents, the reaction proceeded smoothly. Moderate yields and ees have been obtained when the active electron-withdrawing substituents have been positioned on the para to \( R^1 \). Electron-withdrawing substituents afforded increased yields than the electron-donating derivatives. Considerably, the aliphatic substrate \( 13o \) gave the desired product \( 106o \) with a good yield and high enantioselectivity. In a former report, shifting the substituent group to the 4-position of \( N \)-methyl isatin

Fig. 3. An ideal position for the presumed ternary transition state.

Scheme 30. \( F-C \) reaction of indole: Generality of this reaction using a,b-unsaturated 2-aroyl imidazoles.

Scheme 31. Substrate scope with \( (Z) \)-aryl-2-nitroacrylic esters and indoles using catalyst \( \alpha-(RR)-Ir \).

Scheme 32. AF-CA of pyrrole and \( \beta,\gamma \)-unsaturated a-ketoester derivatives.
showed a negative influence on the reactivity, even some reaction did not take place, at all [51]. Once N-benzyl isatin has been applied in place of N-methyl isatin, the reaction with pyrrole proceeded, smoothly to afford the product 109 in high yield and enantioselectivity (Scheme 33, Table 12) [50].

A Probable mechanism for the FC-A reaction of isatin and pyrrole is shown in Scheme 34.

The NH group possibly provided a hydrogen bond with the catalyst 108. The addition of HFIP preferred this reaction. Perhaps HFIP can favor the hydrogen bond of NH of isatin with the catalyst 108 due to the weak Bronsted acidity of HFIP [52]. Relied on these outcomes and the preceding mechanism investigation, a hypothetical bifunctional manner of action in the transition state has been suggested (Fig. 4). The isatin has been stimulated through chelating with a metal center in the catalyst system, whereas the NH in pyrrole worked as a hydrogen bond donating substituent to direct the alkylation reaction at the Si face of isatin.

The rate ratio of various Cu(II)–bis(oxazoline) systems [53] for catalytic reaction has been evaluated in a facile competitive test. The cumulated product enantioselectivity obtained from by using a mixture of catalysts along with antipodal chiral induction. That gave adequate evidence to identify the relative rates in the AF-CA of indoles and benzylidene malonate derivatives. The discovery of non-linear influences in the reaction examined, gave a good insight into the potent and resting positions of the catalysts [54]. Bis(oxazoline) [55], and azabis(oxazoline) [56], effectively mediated the reaction of indole 4 and benzylidene malonate 113a to give the expected product in very satisfactory yield and high enantioselectivity using the precondition that a ligand-metal-ratio of 1:0.5 is exactly kept [57]. Therefore, both ligands seem equally suited by the analysis of the obtained results. In this reaction the kinetic test, using, a small ligand excess with respect to metal salt is not suggestive, since it is presumed favoring the stronger coordinating ligand. Thus, the catalysis should be accomplished at a sub-optimal ligand/metal-ratio of 1.0. A majority of i-Pr-functionalized ligands 114 and 115a was used to obtain a satisfactory enantioselectivity. Extended reaction times resulted in the maximum transformation. High selectivities were obtained, using numerous 4-functionalized benzylidene malonate derivatives 113b-d to react with i-Pr–BOX (R,R)-114 and i-Pr–AzaBOX (S,S)-115a. The ee values obtained from immobilized azabis(oxazoline) (SS)-116 [58] were marginally lower with respects to both the yield and ee, once compared with those of the non-supported counterpart (Scheme 35, Table 13) [54].

In 2014, Zhang and co-workers reported catalytic asymmetric AF-CA transformation of nitroalkenes and indoles by employing an efficient trinuclear Cu2Eu complex catalyst relied on the facile chiral ligand, reduced Schiff base 118, to provide the F–C products with up to 80% ee value and 88% yield [59]. This trinuclear Cu/Eu/Cu complex catalyst is not air-sensitive and can be made in situ through a simple solution self-assembly throughout the catalytic AF-CA reaction.

Based on this method, different substituted nitroalkenes 89, having both electron-donating and electron-withdrawing substituted have been considered. Moderate ee and yield have been detected for the providing products with 4a. Nitroalkenes containing heteroaryl groups accomplished the alkylation with moderately improved outcomes. Remarkably, satisfactory to good enantioselectivity and good yields have been provided for diverse nitroalkenes. It should be mentioned that 2-thiophene afforded the uppermost enantioselectivity (80%). While F–C adduct 119a has been provided with moderately poor ee. Consequently, the absolute configuration of products 119 has been identified to be S (Scheme 36, Table 14) [59].

Extremely significant dinuclear Cu system mediated AF-CA transformation was developed for the alkylation reaction of 1-naphthyl utilizing N-tosyl aldimine. In this route, different chiral amino alcohol obtained Schiff base ligands containing various achiral and chiral linkers have been provided and their Cu (II) systems have been made in situ. One of the dinuclear Cu systems having chiral linker has appeared as a significant catalyst and for

### Table 11

| Entry | $R_1$, $R_2$ | Yield (%) | ee (%) |
|-------|--------------|-----------|--------|
| 1     | Ph, iPr (13a)| 89        | 98     |
| 2     | p-MeC6H4, iPr (13b)| 73 | 96 |
| 3     | p-MeOC6H4, iPr (13c)| 63 | 94 |
| 4     | p-FC6H4, iPr (13d)| 79 | 97 |
| 5     | p-C6H4-NO2, iPr (13e)| 84 | 91 |
| 6     | p-BrC6H4, iPr (13f)| 79 | 94 |
| 7     | o-C6H4OH, iPr (13g)| 96 | 96 |
| 8     | p-FCC6H4, iPr (13h)| 86 | 94 |
| 9     | m-C6H4-NO2, iPr (13i)| 82 | 96 |
| 10    | o-C6H4-Cl, Et (13j)| 72 | 89 |
| 11    | m-BrC6H4, iPr (13k)| 84 | 98 |
| 12    | o-BrC6H4, Et (13l)| 85 | 96 |
| 13    | 2-naphthyl, iPr (13m)| 84 | 96 |
| 14    | 2-thienyl, iPr (13n)| 66 | 94 |
| 15    | phenylpropyl, Et (13o)| 66 | 94 |
| 16    | Ph, Me (13p)| 87 | 96 |
| 17    | Ph, Et (13q)| 80 | 94 |
| 18    | Ph, Bn (13r)| 80 | 95 |
| 19    | Ph, t-Bu (13s)| 70 | 95 |

### Table 12

| Entry | $R_1$ | $R_2$ | Yield (%) | ee (%) |
|-------|-------|-------|------------|--------|
| 1     | H     | Me    | 96         | 99     |
| 2     | 5-F   | Me    | 97         | 98     |
| 3     | 5-Cl  | Me    | 99         | 99     |
| 4     | 5-Br  | Me    | 95         | 98     |
| 5     | 5-I   | Me    | 97         | 91     |
| 6     | 5-O2N | Me    | 98         | 94     |
| 7     | 5-Me  | Me    | 98         | 99     |
| 8     | 6-Br  | Me    | 97         | 99     |
| 9     | 7-Br  | Me    | 96         | 99     |
| 10    | 7-F   | Me    | 93         | 88     |
| 11    | 7-C6F5| Me    | 94         | 82     |
| 12    | H     | Bn    | 97         | 91     |
| 13    | H     | H     | 99         | 69     |
| 14    | 5-Me  | H     | 91         | 63     |
| 15    | 5-Br  | H     | 95         | 56     |
the corresponding arene adducts in very moderate yields (up to 98%) and with high ee (up to 99%). To examine the broad usage of the catalyst Cu(II)-122, F–C-type alkylation reaction of numerous alkyl and aryl tosyl aldimines with 1-naphthol have been happen based on the optimal results. In all the derivatives, the active dinuclear Cu(II)-122 catalyst readily mediated the transformation and afforded the adducts in satisfactory to high yield (78–98%).

Tosyl aldimines without any substitutions in aryl group produced satisfactory yield and excellent ee. The electron withdrawing groups at meta and para position of the derivatives afforded the corresponding adducts with high ee and yields. Although, the electron-withdrawing substituent at ortho position completed moderate ee and good chemical yields. But the substrates having electron donating substituent displayed merely minimal influence

![Scheme 34. A Probable mechanism for the FC-A reaction.](image)

**Table 13**

| Entry | Ligand | R | Yield (%) | ee (%) |
|-------|--------|---|-----------|--------|
| 1     | (R,R)-114 | H | 89        | 99 (R) |
| 2     | (R,R)-114 | H | 97        | 98 (R) |
| 3     | (R,R)-114 | H | 93        | 90 (R) |
| 4     | (S,S)-115a | H | 90        | 98 (S) |
| 5     | (S,S)-115a | H | 90        | 98 (S) |
| 6     | (S,S)-115a | H | 90        | 81 (S) |
| 7     | (R,R)-115d | H | 63        | 97 (R) |
| 8     | (R,R)-114 | Cl | 84        | 80 (R) |
| 9     | (S,S)-115a | Cl | 87        | 76 (S) |
| 10    | (R,R)-114 | Me | 79        | 84 (R) |
| 11    | (R,R)-114 | MeO | 66        | 78 (S) |
| 12    | (R,R)-114 | MeO | 80        | 83 (R) |
| 13    | (S,S)-115a | MeO | 47        | 71 (S) |
| 14    | (S,S)-116 | H | 81        | 87 (S) |

![Scheme 36. Catalytic AF-C reaction of various indoles and nitroalkenes.](image)

**Table 14**

| Entry | R | R’ | Yield (%) | ee (%) |
|-------|---|----|-----------|--------|
| 1     | H | Ph (89a) | 62 (119aa) | 55 |
| 2     | H | 4-FC6H5 (89b) | 52 (119ab) | 63 |
| 3     | H | 4-C6H4Cl (89c) | 67 (119ac) | 53 |
| 4     | H | 4-BrC6H4 (89d) | 65 (119ad) | 53 |
| 5     | H | 4-MeOC6H4 (89e) | 53 (119ae) | 49 |
| 6     | H | 2-furyl (89f) | 72 (119af) | 63 |
| 7     | H | 2-thiophenyl (89g) | 87 (119ag) | 70 |
| 8     | Me | Ph (89a) | 86 (119ba) | 53 |
| 9     | Me | 4-FC6H4 (89b) | 88 (119bb) | 71 |
| 10    | Me | 4-C6H4Cl (89c) | 82 (119bc) | 63 |
| 11    | Me | 4-BrC6H4 (89d) | 76 (119bd) | 64 |
| 12    | Me | 4-MeOC6H4 (89e) | 68 (119be) | 74 |
| 13    | Me | 2-furyl (89f) | 72 (119bf) | 79 |
| 14    | Me | 2-thiophenyl (89g) | 63 (119bg) | 80 |
both on ee and chemical yield. Moreover, this catalytic method functioned well for aliphatic aldimine and 1-naphthol derivatives. Moreover, asymmetric F–C-type alkylation reaction of tosyl aldimine and 2-naphthol has been happen to prolong the usage of the catalytic method. Pleasingly, the similar catalyst afforded corresponding substituted 2-naphthols in moderate yield and ee. (Scheme 37, Table 15) [60].

The AF-CA reaction of pyrrole and nitroalkenes has been catalyzed by using copper (II) bromide and bisphenol A-obtained as chiral catalyst [61] at ambient temperature. The catalyst was realized to be appropriate for the AF-C-type alkylation reaction of pyrrole and a variety of nitroalkenes, giving optically active alkylated pyrroles having up to 94% ee. Moreover, enantiomerically pure 3-nitro-2-arylpropanamides have been synthesized through the oxidative cleavage of the pyrrole rings in the F–C adducts with NaIO4/RuCl3 to exhibit the synthetic use of the adducts. The generality and restrictions of this catalytic transformation have been considered by using the AF-CA transformation of pyrrole and a number of nitroalkenes 89. Nitroalkenes 89 containing electron-donating or electron-withdrawing substituents on diverse situations of the phenyl ring have been transformed into the AF-CA adducts having excellent mass balances and conversions. The treatments of nitroalkenes having a MeO substituent at para- or ortho-situation of the phenyl ring exhibited expressively lesser yield than the treatment of nitrostyrenes having an electron-donating or electron-withdrawing substituent. The AF-CA adducts have been provided with moderate to high ee, regardless of whether the substituent was electron-donating or electron-withdrawing. Ortho-group on the phenyl ring of the nitroalkene, both methoxy and nitro substituents, provided the lesser ees of 79% and 67%, respectively, demonstrating that a growth in the size of the ortho substituent has an adverse influence on the ee. AF-CA adducts 126a, d, g, and r may be recrystallized as single enantiomers (Scheme 38, Table 16) [62].

It was suggested a stereochemical transition state for this treatment relied on the experimental consequences and the configurations of the compounds. As presented in Fig. 5, the bisphenol A-Cu system acts as a bifunctional catalyst. The Cu2+ ion has been linked to the nitroalkene via the oxygen atom of the \( \text{NO}_2 \) substituent, although the pyrrole substrate has been motivated through H-bonding between and the phenolic oxygen atom and the pyrrole nitrogen proton of the system. The favored attack of pyrrole on the Si face of nitroalkene would provide the S-configured compound [62].

A F-CA reaction of styrenes and trifluoropyruvates using NiClO4·6H2O/bipyridine system as an efficient catalyst provided allylic alcohols in high yields. The enantioselective reaction has been mediated by chiral copper(I) triflate/bisoxazoline system to give the desired chiral allylic alcohol derivatives containing trifluoromethylated quaternary stereogenic centers in good ees (up to 75%) [63]. Upon systematic surveys of Lewis acids, chiral ligands,

### Table 15
Asymmetric addition of 1-naphthol or 2-naphthol with tosyl aldimine with dinuclear Cu(II)-122 catalyst.

| Entry | X, Y, Z, R | Yield (%) | ee (%) |
|-------|------------|-----------|--------|
| 1     | HO, H, H, 3-O2NC6H4 | 98        | 99 (123a) |
| 2     | HO, H, H, 4-O2NC6H4 | 95        | 96 (123b) |
| 3     | HO, H, H, 4-BrC6H4  | 84        | 96 (123c) |
| 4     | HO, H, H, 4-BrC6H4  | 95        | 90 (123d) |
| 5     | HO, H, H, 2-ClC6H4  | 80        | 88 (123e) |
| 6     | HO, H, H, 4-ClC6H4  | 90        | 96 (123f) |
| 7     | HO, H, H, Ph       | 82        | 92 (123g) |
| 8     | HO, H, H, 2-MeC6H4  | 79        | 85 (123h) |
| 9     | HO, H, H, 4-MeOC6H4 | 82        | 90 (123i) |
| 10    | HO, H, H, 4-MeC6H4  | 80        | 92 (123j) |
| 11    | HO, H, H, nC3H7    | 70        | 78 (123k) |
| 12    | HO, H, H, 3-O2NC6H4 | 95        | 96 (123l) |
| 13    | HO, H, MeO, 3-O2NC6H4 | 85   | 93 (123m) |

Scheme 37. Asymmetric addition of 1-naphthol or 2-naphthol with tosyl aldimine with dinuclear Cu(II)-122 catalyst.

Scheme 38. Catalytic AF-CA of pyrrole 7 with various nitroalkenes.
and different solvents, the system of copper(II)triflate with a chiral bisoxazoline ligand 129 was found as a catalyst of choice for the effective enantioselective alkenylation of trifluoropyruvates, which induced merely good enantioselectivity to the products. Then, numerous styrene derivatives have been tested to reveal the generality of the enantioselective reactions. All of the cases gave the desired products in good ee values (64–75%). Although, the yields have been disapprovingly influenced by the electron-withdrawing substituents, that led to low to good yields for the corresponding products 130ae-ag and 130ai. On the other hand, styrene derivatives containing electron-donating substituents supplied the desired products 130aa-ac, 130ah, 130al, 130aq, and 130ar) in moderately upper yield and with the similar value of enantioselectivity (70%). Besides, product 130ao provided from the transformation of 1,1’-diphenylethene with 128 has been separated in 56% yield and 68% enantioselectivity (Scheme 39) [63].

An extremely AF-CA of indole derivatives and N-sulfonfyl aziridine derivatives as alkylation agents was achieved by using the system of Cu-(CH3CN)6BF4/(S)-Segphos as a catalyst [64]. Various optically active tryptamines were provided in moderate to high yields and ees through a kinetic resolution method. Based on this approach, numerous racemic 2-aryl-N-tosylaziridine derivatives 131 treated easily with N-allylindole 4a to give the corresponding products in satisfactory yields and moderate to high ees. Various substituents on the benzene ring of N-tosylaziridine derivatives 131 were well-endured, while the ees were affected disapprovingly by the electron-donating groups. The enantioselectivity levels for products 133-e-h bearing electron-donating substituents were marginally poorer than those of products 133-d and 133i which contain electron-withdrawing groups. Furthermore, a poorer but moderate enantioselectivity has been detected for the transformation of 2-naphthyl-functionalized N-tosylaziridine 131k. Also, the reaction of aziridine 131j having an orthomethylphenyl substituent resulted in desired product 133j in 87% ee, demonstrating that enantioselectivity was influenced by steric hindrance (Scheme 40, Table 17) [64].

Various heteroarylidene malonate obtained bis(thiazoline) ligands (135a and 135b) [65] have been used to a F–C reaction of indole 5 and alkylidene malonate 113. The copper(II)triflate system of ligand 136 containing a benzyl group gave good to high enantioselectivity for the products [66]. EtOH has been applied as the solvent in the next examination because of its low price and the same excellent ee. The generality of the 136-copper(II)triflate system in F-CA has been tested by utilizing different structurally indoles and arylidene malonate derivatives. In most cases, the reaction proceeded more sluggishly in comparison with those of their bis(oxazoline) analogues, and besides the extended time reaction times were required to attain satisfactory to excellent yield. Outstanding outcomes have been provided for the three substrates with 4-MePh, 4-MeOPh, and 4-FPh substituents (99% yield and 98–99.5% enantioselectivity). These enantioselectivity were the best, accomplished in an enantioselective reaction mediated by thiazoline-including ligands till 2011. Although, for substrates having both a 3-Br and a 2-Cl substituent on phenyl group the enantioselectivity reduced to 75% and 71%, respectively. Satisfactory to good ees have been provided for the products of the benzylidene malonate treating with 5-MeO-indole, 5-Me-indole, 5-Cl-indole, 6-Cl-indole, N–Me-indole, and N-benzylindole, demonstrating that the groups on indole ring show a remarkable influence on the enantioselectivity (Scheme 41, Table 18) [66].

Wang and co-workers in 2011 reported a facile and extremely significant catalytic complex for the AF-C-alkylation reaction of pyrrole derivatives and nitroalkene derivatives [67]. Various optically active pyrrole derivatives were formed in excellent yields and high ees based on catalysis of a novel tridentate Schiff base-Cu...
Extremely moderate regioselectivities have been detected between alkylation of the 2 or 5 position, particularly if 3-functionalized or 3,4-difunctionalized pyrrole derivatives have been applied in this reaction [67]. Nitroalkene derivatives having both electron-withdrawing or donating substituents at the ortho position of the aromatic ring treated easily with pyrrole, providing the desired products with high enantioselectivity. Excellent enantioselectivities have been provided in all reactions, while electron-rich nitroalkene derivatives gave the corresponding products in reduced yields. Considerably, high chemical yields and ee's have been provided using different aliphatic nitroalkene derivatives, bearing masked hydroxyl substituents. The catalyst obtained from (R)-139 exhibited the similar reactivity to the current reaction, giving the corresponding product 140ay in 94% enantioselectivity and the opposite configuration to 140am. Remarkably, if the reactions have been achieved in the mixed solvent of toluene and water (9:1), moderate yields and high ees have been preserved in most situations, despite the background reaction in H2O (Scheme 42, Table 19) [67].

The remarkable chiral bis(oxazoline) ligands 141 have been suitably provided in four steps [68]. In 2011, Chen and co-workers reported the preparation of range of novel and facile C2-symmetric diphenylmethylidene malonate-type bis(oxazoline)
ligands and employed them successfully in AF-CA of allylic substrates [69]. This catalyst 141 was employed in the AF-CA of indoles by alkylidene malonate 135, which gave the corresponding alkylated products in satisfactory yields and high to excellent ee value (up to > 99%). The 141-copper (II) triflate catalyst was applied in AF-CA reaction of a series of structurally various indoles and arylidene malonates. The benzylidene malonates including either electron-donating and electron-withdrawing groups at the para-position was reacted with indole to give the alkylation adducts in high chemical yields and ee. The excellent ee was provided in the case of F-substituted benzylidene malonates due to the smaller size of fluorine than chlorine and methyl group (>99% enantioselectivity). The considerable changes in ee values were observed for diverse substituted indoles. Commonly, introduction of electron-withdrawing substituent to indole led to low enantioselectivity. For indoles bearing electron-releasing substituent, such as, 5-methoxy indole, excellent yield and high ee (98%) along with excellent chemical yield 99% was observed (Scheme 43, Table 20) [69].

You and co-workers in 2011 demonstrated that heteroarylidene malonate-bis(oxazoline) ligand with furan and thiophene units on the double bond provided excellent asymmetric catalyst in the Cu(II) catalyzed F-CA of indole derivatives with arylidene malonates (up to 99% yield and >99% ee) [70]. The asymmetric AF-CA reaction of indoles to N-sulfonyl aldimines has been surveyed by utilizing a heteroarylidene malonate-type bis(oxazoline) as a chiral ligand. Excellent ee value (up to >99%) have been accomplished by utilizing the combination of Cu (II)-144 and a benzyl substituent. Following this methodology a series of indoles and aldimines have been prepared as shown Scheme 44 [70]. Once R2 was a p-MeO substituent on the aromatic ring, the transformation was very slow even if the reaction time was extended to 96 h. Seemingly, the electron-withdrawing group on the aromatic ring of the aldimine is serious for excellent catalytic performance. The electron-donating group on the aromatic ring can improve the electron density of the carbon atom of the C=O bond, decrease its electrophilicity, and therefore fewer reactivity of the AF-CA transformation. It is remarkable that this catalyst presented an abundant upper yield than previous bis(oxazoline)-Cu(II) complexes. For all of the aldimine substrates having electron-withdrawing substituents at the p-, m-, and o-position of the aromatic ring, the F-C transformation created high to excellent ee value between 88 and 96% enantioselectivity. Groups at the meta- or ortho-position had slight to no influence on the reactivity or ee. However, the treatment of indole and N-benzylidene-4-methylbenzene sulfonamide 143 was slower than those with other N-sulfonyl imines having electron-withdrawing substituents, the corresponding products was also generated in 70% yield and with 90%. The treatment of N-(4-(CF3) benzylidene)-4-methylbenzene sulfonamide 143n-q and 5-methoxyindole, 5-methylindole, 5-chloroindole, and 6-chloroindole afforded the corresponding products in high yields.
and enantioselectivity. It has been realized that indoles having electron-deficient substituents afforded upper ee than those with electron-donating substituents, particularly in the case of 6-chloroindole (>99% ee) (Table 21) [70].

Based on the transformation mechanism, Zhou and co-workers have shown a transition-state model for this kind of catalytic F–C amidolkylation transformation that probably presented the 1,3-binding mode of the nitrogen atom of the imine and the oxygen atom of the sulfonyl linked to the Cu center. Examining the similarities of the two types of ligand framework, both catalytic methods of the BOX-Cu(II) complex can show the same catalytic mechanism as presented in Fig. 6. Although this catalyst afforded a greater catalytic efficacy and similar ee in contrast with Zhou’s report, consequently representing which the ligand’s structure demonstrates a significant role in the catalytic method. For this catalyst the upper catalytic efficacy might be related to the electronic effect that is the consequence of the heterocycle scaffold (furan or thiophene) linked to the double bond. As for the ee, the benzyl substituent on the oxazoline ring is an essential factor for attaining the excellent ee in the procedure of stereoselective induction [70].

Chiral bis(sulfonamide)-diamine [71] worked as an efficient kind of ligand for a copper(I)triflate-mediated AF-CA reaction of indoles and nitroalkene derivatives. The corresponding products have been provided with up to 99% yield and 97% enantioselectivity [72]. Based on the optimization results, the generality of the reaction was examined. As exhibited in Table 22, in spite of steric hindrance or electronic influences of different aryl groups, aromatic nitroalkene derivatives treated with indole 4 and gave the desired products in high yields and ees. Notably, various complexes catalyzed this reaction giving lower ees because of steric hindrance on ortho group of the phenyl substituent of aromatic nitroalkene derivatives. In contrast, using this complex, the enantioselectivity improved by comparison of occurrence of ortho substitution. Besides, when heteroaromatic nitroalkene derivatives were used in this reaction moderate ees were obtained. Unfortunately, when aliphatic nitroalkene derivatives have been utilized in this reaction, the outcomes turned out to be not as promising as the result of aromatic nitroalkene derivatives. About 20 mol% catalyst was required once (E)-1-nitro-1-hexene 89p was used as the substrate, and merely a good yield and enantioselectivity have been provided (Scheme 45) [72].

An asymmetric alkylation reaction of indole derivatives and trifluoroethylidene malonates mediated by Cu(I)-bis (oxazoline) systems [73] was achieved in 2011 by Lu and co-workers [74]. The desired products with a stereogenic tertiary carbon center containing a trifluoromethyl substituent have been produced in high yields and enantioselectivity. The synthetic usefulness of this enantioselective catalytic reaction has been shown through the formation of β-CF3–tryptophan and 4-CF3–β-caroline in excellent enantioselectivity [74]. The generality of the AF-CA reaction was examined by using various indole derivatives and trifluoroethylidene malonates. Indole derivatives bearing both electron-donating and withdrawing groups were all appropriate substrates, manufacturing the corresponding CF3-functionalized indoles in high chemical yields and moderate ees. The reaction of an electron-rich indole having methoxyl group advanced quickly even at −50 °C to afford the expected products in excellent yields and high optical purity. Reactions of methyl-functionalized indole at the

**Table 21**

| Entry | R1 | R2 | Yield (%) ee (%) |
|-------|----|----|------------------|
| 1     | H  | p-F (143b) | 80 (145b) | 94 |
| 2     | H  | p-Cl (143c) | 82 (145c) | 91 |
| 3     | H  | p-Br (143d) | 90 (145d) | 93 |
| 4     | H  | p-NC (143e) | 85 (145e) | 95 |
| 5     | H  | p-F (143f) | 85 (145f) | 96 |
| 6     | H  | m-O2N (143g) | 81 (145g) | 89 |
| 7     | H  | m-NC (143h) | 90 (145h) | 94 |
| 8     | H  | m-Br (143i) | 85 (145i) | 90 |
| 9     | H  | m-FC (143j) | 84 (145j) | 88 |
| 10    | H  | o-FC (143k) | 80 (145k) | 99 |
| 11    | H  | H (143l) | 70 (145l) | 90 |
| 12    | H  | p-MeO (143m) | 0 (145m) | — |
| 13    | 5-Me | p-F (143n) | 85 (145n) | 91 |
| 14    | 5-Me | p-F (143o) | 80 (145o) | 95 |
| 15    | 5-Cl | p-F (143p) | 82 (145p) | 97 |
| 16    | 6-Cl | p-F (143q) | 86 (145q) | >99 |

**Table 22**

| Entry | R1 | R2 | Yield (%) ee (%) |
|-------|----|----|------------------|
| 1     | H  | Ph (89a) | 99 (148a) | 95 (R) |
| 2     | H  | 4-ClC6H4 (89b) | 96 (148b) | 92 |
| 3     | H  | 3-ClC6H4 (89c) | 94 (148c) | 94 |
| 4     | H  | 2-ClC6H4 (89d) | 99 (148d) | 97 |
| 5     | H  | 4-MeC6H4 (89e) | 99 (148e) | 93 |
| 6     | H  | 4-MeOC6H4 (89f) | 99 (148f) | 88 |
| 7     | H  | 2-MeOC6H4 (89g) | 96 (148g) | 93 |
| 8     | H  | 2-BrC6H4 (89h) | 97 (148h) | 96 |
| 9     | H  | 3-BrC6H4 (89i) | 99 (148i) | 93 |
| 10    | H  | 4-BrC6H4 (89j) | 96 (148j) | 92 |
| 11    | H  | 2-FC6H4 (89k) | 98 (148k) | 96 |
| 12    | H  | 3-FC6H4 (89l) | 99 (148l) | 94 |
| 13    | H  | 2-furyl (89m) | 98 (148m) | 88 |
| 14    | H  | 1-naphthyl (89n) | 95 (148n) | 95 |
| 15    | H  | 2-naphthyl (89o) | 90 (148o) | 93 |
| 16    | H  | nBu (89p) | 65 (148p) | 70 |
| 17    | Me | Ph (89a) | 99 (148q) | 94 |
| 18    | MeO | Ph (89a) | 99 (148r) | 95 |
| 19    | F  | Ph (89a) | 88 (148s) | 94 |
| 20    | Br | Ph (89a) | 99 (148t) | 94 |

**Scheme 45.** The AF-CA of indoles and various nitroalkenes.
7-position advanced with moderate ees (Scheme 46, Table 23) [74].

The facile and inexpensive chiral catalyst, heteroarylidiene-tethered Ph-bis(oxazoline)-copper(II) triflate mediated the AF-CA of indole derivatives and pyrrole with β,γ-unsaturated α-ketoester derivatives. The 3-indolyl products have been provided in high enantioselectivity. Furthermore, the 2-pyrrolyl adducts have been accomplished in up to 92% enantioselectivity for the initial time. Next, under the optimal conditions, different indole derivatives and various functionalized γ-phenyl β,γ-unsaturated α-ketoester derivatives have been tested. The reaction was completed in 30 min. When most of them were used as substrate, excepting for a small number of β,γ-unsaturated α-ketoester derivatives having electron-withdrawing groups for instance 4-CNPh, 4-CF₃Ph, 4-NO₂Ph substituents and indole having –CO₂Me group in six position. (Scheme 47, Table 24) [75].

Successively, the reaction of pyrrole 7 and numerous substituted γ-phenyl β,γ-unsaturated α-ketoester derivatives 105 has been examined. All reactions produced the pyrrole products 154 in 82–99% yields. In all reactions, excellent ees have been provided from 85 to 92% yield, demonstrating that the groups on the phenyl ring contain a minor effect on the enantioselectivity. Remarkably, the reaction has been finished in 5 min by using 5 mol% of the catalyst for many of compounds, excluding for a few of β,γ-unsaturated α-ketoester derivatives having an electron-withdrawing 3-NO₂Ph, 4-FPh or 3-BrPh substituent (Scheme 48, Table 25).

A probable mechanism to clarify the detected outcomes is shown in Fig. 7. The β,γ-unsaturated α-ketoester links to the Cu center in a nearly tetrahedral geometry in the 152-Cu(OTf)₂ system [76], pyrrole attacks the β,γ-unsaturated α-ketoester preferably from the Si face, providing the production of the main S-configured product. Moreover, the similar transition might be assumed for the treatment of indole. The observed higher reactivity might be related to the electronic influence of oxazoline rings tethered to the heteroarylidiene scaffold, and the excellent enantioselectivity provided from the well-defined chiral situation around the Cu center.

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### Table 24

| Entry | R   | R¹   | Yield (%) | ee (%) |
|-------|-----|------|-----------|--------|
| 1     | H   | Et   | 96 (151a) | 90     |
| 2     | H   | Bn   | 99 (151b) | 90     |
| 3     | H   | Me   | 99 (151c) | 90     |
| 4     | 5-Me| Et   | 92 (151d) | 92     |
| 5     | 5-Me| Bn   | 98 (151e) | 90     |
| 6     | 5-Me| Me   | 96 (151f) | 90     |
| 7     | 7-Me| Et   | 97 (151g) | 91     |
| 8     | 7-Me| Bn   | 98 (151h) | 93     |
| 9     | 7-Me| Me   | 99 (151i) | 96     |
| 10    | 6-Br| Et   | 90 (151j) | 86     |
| 11    | 6-Br| Bn   | 84 (151k) | 84     |
| 12    | 6-Br| Me   | 95 (151l) | 86     |
| 13    | 5-O₂N| Bn | 91 (151m) | 75     |
| 14    | 5-O₂N| Me | 98 (151n) | 79     |
| 15    | —   | Bn   | 70 (151o) | 16     |

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### Scheme 46

Catalytic AF-C reactions of indoles 4 and trifluoroethylene malonates 149.

### Scheme 47

Reactions of various indoles and β,γ-unsaturated α-ketoesters.

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### Scheme 48

Reactions of pyrrole with β,γ-unsaturated α-ketoesters.
Both the phenyl substituent on the oxazoline ring, and the remote thiopehe scaffold tethered to the double bond and the asymmetry of the current catalyst show a supportive effect on the observed high enantioselectivity [75].

The gluosamine obtained gluco BOX-Cu(II) [77] system has been known to be a distinctive catalytic complex for AF-CA of indoles and 2-enopyridine-1-oxide derivatives. Various 3-alkylated indoles have been formed by using gluco BOX-Cu(II) system in high yields with excellent enantioselectivity up to 99% [76]. The generality and restrictions of the AF-CA reaction have been explored by using copper(II) triflate-157 [79] system. The alkylation was accomplished easily with different indole derivatives to give the desired 3-alkylated indole derivatives in excellent yields and high enantioselectivity. For example, 5-bromoindole afforded the 3-alkylated indole derivatives in 88% yield and 90% enantioselectivity. Also, 5-chloroindole generated the Michael adduct with excellent enantioselectivity up to 99% [78]. The alkylation reaction of indole to various indoles and 2-enoylpyridine-1-oxide derivatives. Various 3-alkylated indoles and 2-enoylpyridine-1-oxide derivatives. Various 3-alkylated indoles have been known to be a distinctive catalytic complex for AF-CA of indoles [78].

A probable transition state model for the AF-CA reaction was shown in Fig. 8. The poor enantioselectivity of N-methylindole can be attributed to the relative inaccessibility of the nitrogen-hydrogen substituent for hydrogen bonding with the acetate scaffold in the suggested transition state model. The poor enantioselectivity of pyrrole in F-CA assists the reaction proceeds via such transition state. However, the hydrogen bonding occurs between catalyst and pyrrole, the π-orbital of pyrrole, that was included in F-CA, is different from that of indole derivatives [78].

A wide range of chiral ligands having an imidazole-oxazoline scaffold were reported as novel kind of non-symmetric N,N-bidentate ligands. All the chiral ligands have been synthesized starting enantiomerically pure (S)-2-amino-3-methyl-1-butanol and 2,2-diethylmalonic acid in four stages with high optical purity. These ligands remarkably affect the Cu-mediated asymmetric addition reaction of indole to 2,2-unsaturated ketones, affording the expected products in excellent ee and moderate yield [80]. The fine-tuning capability of these ligands exhibited an imperative role in attaining excellent ee in the stereoselective alkylation (up to 99% ee). The improved ee of the treatment might be because of the activation and stereoselective induction of chiral Lewis acid metal complex linked by using enones via a concerted mechanism of 1,4-metal bonding model. To demonstrate the scope of this stereoselective AF-CA reaction of indole, and different substrates 160b-I, several instances have been occurred by using ligand 161 10 mol % and 20 mol % of copper(II) triflate in acetonitrile at ambient temperature and the consequences were presented in Scheme 50. It

| Entry | R<sup>1</sup> | R<sup>2</sup>, R<sup>3</sup> | Yield (%) | ee (%) |
|-------|-------------|----------------|----------|-------|
| 1     | 4-ClC<sub>6</sub>H<sub>5</sub> (156a) | H, H | 94 (158a) | 97    |
| 2     | 4-ClC<sub>6</sub>H<sub>5</sub> (156a) | 5-Br, H | 88 (158b) | 90    |
| 3     | 4-ClC<sub>6</sub>H<sub>5</sub> (156a) | 5-Cl, H | 94 (158c) | 94    |
| 4     | 4-ClC<sub>6</sub>H<sub>5</sub> (156a) | 5-MeO, Me | 94 (158d) | 85    |
| 5     | 4-ClC<sub>6</sub>H<sub>5</sub> (156a) | H, H | 88 (158e) | 77    |
| 6     | Ph (156b) | H, H | 97 (158f) | 99    |
| 7     | Ph (156b) | 5-Br, H | 91 (158g) | 93    |
| 8     | Ph (156b) | 5-Cl, H | 94 (158h) | 92    |
| 9     | Ph (156b) | H, Me | 84 (158i) | 70    |
| 10    | 4-OMeC<sub>6</sub>H<sub>5</sub> (156c) | H, H | 98 (158j) | 96    |
| 11    | 4-MeC<sub>6</sub>H<sub>4</sub> (156d) | H, H | 87 (158k) | 94    |
| 12    | 4-FC<sub>6</sub>H<sub>5</sub> (156e) | H, H | 94 (158k) | 95    |
| 13    | 4-BrC<sub>6</sub>H<sub>5</sub> (156f) | H, H | 91 (158m) | 92    |
| 14    | 4-FC<sub>6</sub>H<sub>5</sub> (156g) | H, H | 92 (158n) | 99    |
| 15    | 4-ClC<sub>6</sub>H<sub>5</sub> (156h) | H, H | 98 (158o) | 94    |
| 16    | 2-ON-C<sub>6</sub>H<sub>4</sub> (156i) | H, H | 96 (158p) | 98    |
| 17    | 3-ClC<sub>6</sub>H<sub>4</sub> (156j) | H, H | 94 (158q) | 96    |
| 18    | 3-ClC<sub>6</sub>H<sub>4</sub> (156k) | H, H | 94 (158r) | 99    |
| 19    | 2-furyl (156l) | H, H | 91 (158s) | 94    |
| 20    | 1-naphthyl (156m) | H, H | 88 (158t) | 90    |
| 21    | 8β (156n) | H, H | 65 (158u) | 33    |
| 22    | Cyclohexyl (156o) | H, H | Trace (158v) | n.d. |

Scheme 49. AF-C reaction of various indoles and 2-enopyridine-N-oxides.

Scheme 50. Highly AF-C reactions of indoles with 2,2-unsaturated enones mediated by ligand 161-Cu(OTf)<sub>2</sub>
Excellent yields and advanced with 98% yield and merely 34% enantioselectivity (primarily, once ethylidene malonate has been used, the reaction ring and heterocyclic arylidene malonates worked as substrates arylidene malonate. Furthermore, difunctionalized, condensed-meta-directing the another apical location. Arylidene malonate was atom in apical space and both carboxyl scaffolds of arylidene ligand take three coordinate situations in which one nitrogen atom that coordinates with the tosyl group. Therefore, the ability of this nitrogen atom linking with copper(II) center is reduced. A distorted octahedral geometry at Cu center [82] is taken into consideration in which the remaining three nitrogen atoms of ligand Cu(II)-167,arylidene malonates and indole derivatives have been examined. Both steric and electronic property hindrance on arylidene malonate has been endured (164a-m). This reaction gave the desired products in high yields and ees, in spite of electron-withdrawing or donating substruents on the para- (164b-g), meta- (164h-j) or ortho-position (164k-m) of the aromatic ring in arylidene malonate. Furthermore, difunctionalized, condensed-ring and heterocyclic arylidene malonates worked as substrates for this conversion but with faintly poorer ees (164n-p). Inappropriately, once ethyldiene malonate has been used, the reaction advanced with 98% yield and merely 34% enantioselectivity (164q).

Excellent yields and ees have been provided in the case of indole derivatives including electron-withdrawing or donating substituents at 5, 6 or 7 position (164r-u) (Scheme 51) [81].

A probable model for the Cu-mediated AF-CA of indoles 4 and various arylidene malonates 113 is exhibited in Fig. 9. Catalyst Cu(OTf)2 triflate serves in a bifunctional method. A weak hydrogen bonding was provided between indolic proton and the nitrogen atom that coordinates with the tosyl group. Therefore, the ability of this nitrogen atom linking with copper(II) center is reduced. A distorted octahedral geometry at Cu center [82] is taken into consideration in which the remaining three nitrogen atoms of ligand 163 take three coordinate situations in which one nitrogen atom in apical space and both carboxyl scaffolds of arylidene malonate occupy two equatorial locations with isobutyl alcohol directing the another apical location. Arylidene malonate was activated via chelating to copper(II) center. Furthermore, the π-π stacking between aryl substituent of arylidene malonate and benzyl substituent R2 of 163 turned the arylidene malonate in a fixed position. One phenyl substituent of (1R,2R)-1,2-diphenylethlylenediamine scaffold protects the back of arylidene malonate, therefore leading the indole to attack on the Re face and give the corresponding product with the configuration of S [81].

Reusable Cu(II) chiral amino alcohol based on Schiff base systems [83] easily mediated the F-CA reaction of indole and aryl aldimine to give the corresponding products in moderate yields and with ees up to 97% [84]. To realize the mechanism of this catalytic F-CA reaction, a kinetic study has been performed using various amounts of the catalyst Cu(II)-167, N-(3-nitrobenzylidene)-4-methylbenzene sulfonamide and indole as a model substrate. The F-CA reaction of N-(3-nitrobenzylidene)-4-methylbenzene sulfonamide was found being first order with respect to the quantity of the catalyst and the concentration of nucleophile and naturally does not depend on the concentration of the substrate (aryl aldimine). To examine the generality of the reaction, different functionalized aldimine derivatives have been reacted with indoles and functionalized indole derivatives as nucleophiles. Commonly, electron-withdrawing groups at the 3 and 4 positions in the phenyl

| Entry | R1, R2 | Yield (%) | ee (%) |
|-------|--------|-----------|--------|
| 1     | p-ClPh, Ph | 84 | 93.8 (S) |
| 2     | p-ClPh, Naphthyl | 81 | 95.6 (S) |
| 3     | 2,4,6-(CH3)3Ph, Ph | 40 | 96.0 (S) |
| 4     | 2,4,6-(CH3)3Ph, Naphthyl | 22 | 97.3 (S) |
| 5     | Toly1, Ph | 73 | 95.7 (S) |
| 6     | Toly1, Naphthyl | 27 | 93.4 (S) |
| 7     | p-MeOPh, Ph | 89 | 96.4 (S) |
| 8     | p-MeOPh, Naphthyl | 66 | 90.8 (S) |
| 9     | Ph, Naphthyl | 47 | 95.5 (S) |
| 10    | Thiophene, Ph | 65 | 89.7 (R) |
| 11    | Ferrocene, Ph | 8 | 87.7 (R) |

Fig. 9. Proposed transition state model of catalyst Cu(II)-167-Cu(OTf)2.
ring of aldimine gave higher enantioselectivity. The electron-donating groups at the similar positions, and enantioselectivity. However, electron withdrawing groups at the 2 position led to products with poor yield and enantioselectivity. In the case of the reaction of indoles with N-benzylidene-4-nitrosourea and N-benzylidene-benzene sulfonamide the ees are comparable with the reaction of N-tosylaldimine derivatives. Although, electron donating groups on the phenyl ring of indole afforded moderate to high yields and ees. An analogous outcome has been provided using an electron withdrawing substituent (89% enantioselectivity), however once applying the N-methyl functionalized indole merely a trace quantity of product has been provided (Scheme 52, Table 28) [84].

Extremely asymmetric catalytic F-CA reactions of cyclic α-alkylidene β-oxo imide derivatives and indole, pyrrole, or furans at comparatively low temperatures were demonstrated in 2015 [85]. The model has been stabilised through an intramolecular hydrogen bond, in which the cyclic α-alkylidene β-oxo imide links with copper(II) through the two imide carbonyls. α-Alkylidene β-oxo imides show an acidic imide hydrogen that provides an intramolecular hydrogen bond (complex 169). Remarkably, this was confirmed by using single crystal X-ray crystallographic and NMR data analysis of methyl (1-methyl-2-oxo-1,2,5,6-tetrahydropyridine-3-carbonyl)carbamate [86]. The intramolecular hydrogen bonding leads to a rigid conformation of system 169; therefore, the two imide carbonyls form a chelate system with the metal cation. Therefore, the two enantiotropic faces of the reacting double bond in system 169 would be evidently distinguished due to its nearing to the bisoxazoline group. β,γ-Unsaturated α-ketoesters have been applied effectively in catalytic AF-C reactions described by Jørgensen et al. [73b] This was related to the bisoxazoline group which significantly protecting one side of the σ-cis double bond in system 170 (Fig. 10). Therefore, F–C reactions through system 169 are expected to demonstrate excellent ee since the reacting double bond is anticipated to be more hindered by the oxazoline group once compared with system 170. The usage of cyclic α-alkylidene β-oxo imides to F-CA of heteroaromatic compounds have also been investigated [85].

The catalytic AF-C reactions of 171 and indole derivatives 4a–g have been explored using an efficient catalyst 172 along with copper(II) triflate in dichloromethane. The enantioselectivity of 173aa reduced ranging from 97% (−60 °C) to 93% (−40 °C). The enantioselectivity of the reaction of indole 4b reduced considerably (68%). This was possibly because of the acidic C1 NH of 4b disturbing the hydrogen bond in 171. The chemical yield and enantioselectivity did not change in the reaction of 1-benzylindole 4c. The reaction of 171 with 1-acetylindole 4d did not take place because of the steric hindrance caused by C5 substituent of indole.

The substituent effect has been detected in the reaction rate; that is, the electron-donating methoxy-enhanced the reaction and the electron-withdrawing MeO2C and Cl reduced the reaction rate. The reaction of 4e proceeded smoothly at −60 °C and the enantioselectivity increased to 95% (Scheme 53, Table 29) [85].

Highly efficient AF-C C2-alkylation reactions of 3-functionalized indole derivatives and α,β-unsaturated esters or nitroalkene derivatives have been achieved with chiral Lewis acids as catalysts that gave chiral indoles containing C2-benzylic stereogenic centers in moderate to high yields and ees [87]. Noticeably, various α,β-unsaturated ester derivatives 175a–h having diverse aryl groups were surveyed. All of the reactions of α,β-unsaturated ester derivatives 175a–h containing both electron-donating and withdrawing groups on the aromatic ring proceeded to completion easily to give the corresponding products in high yields. Ees were usually high, whereas the halo groups (F, Cl, and Br) led to moderately poorer enantioselectivity. Furthermore, 2-naphthyl and heteroaryl substrates 175i–k have been effectively treated with 3-methylindole 4a to supply the desired products 175ai–ak in high yields and moderate to high enantioselectivities. In addition, the substituent effect of 3-functionalized indole has been tested. High yields and moderate ees have been provided for 3-ethyl-, 3-isopropyl-, 3-benzyl-, and 3-phenyl-functionalized indole derivatives 4b–e; though, the reactivity of 4c, 4d, and 4e was comparatively poorer, and an increased catalyst loading has been needed to guarantee high yields. Furthermore, moderate outcomes have been provided for 3-methylindole derivatives bearing both electron-donating and withdrawing groups on the aromatic ring.

| Entry | R1, R2, R3 | R4, R5 | Yield (%) | ee (%) |
|-------|------------|--------|-----------|--------|
| 1     | H, H, H    | 3-O2N/Me | 98 (168a) | 97     |
| 2     | H, H, H    | 4-O2N/Me | 98 (168b) | 92     |
| 3     | H, H, H    | 4-Br/Me  | 90 (168c) | 95     |
| 4     | H, H, H    | 4-NIC/Me | 86 (168d) | 82     |
| 5     | H, H, H    | 2-Cl/Me  | 75 (168e) | 72     |
| 6     | H, H, H    | 3-Cl/Me  | 83 (168f) | 97     |
| 7     | H, H, H    | 4-Cl/Me  | 89 (168g) | 96     |
| 8     | H, H, H    | 2-F/Cl/Me| 70 (168h) | 65     |
| 9     | H, H, H    | 4-F/Cl/Me| 83 (168i) | 94     |
| 10    | H, H, H    | 3-F/Cl/Me| 84 (168j) | 81     |
| 11    | H, H, H    | 4-Me/Me  | 70 (168k) | 81     |
| 12    | H, H, H    | 3-Me/Me  | 68 (168l) | 75     |
| 13    | H, H, H    | 3-Br/H   | 85 (168m) | 89     |
| 14    | H, H, H    | 4-Br/H   | 82 (168n) | 91     |
| 15    | H, H, H    | 4-B/MeO  | 84 (168o) | 96     |
| 16    | H, Me, H   | 3-O2N/Me | 89 (168p) | 92     |
| 17    | H, Me, H   | 3-O2N/Me | 78 (168q) | 80     |
| 18    | H, H, F    | 3-O2N/Me | 85 (168r) | 89     |
| 19    | Me, H, H   | 3-O2N/Me | Trace     |        |

Table 28

The F-CA of various aldimines with indoles and substituted indoles.

Scheme 52. The F-CA of various aldimines with indoles and substituted indoles.

Fig. 10. Suggested structures of systems 169 and 170.
The absolute configuration of bromo-product 176 ab has been identified to be S relied on its single-crystal X-ray structure. As demonstrated in Fig. 11, a suggested model for enantioselective induction was presented. Substrate 175b in the presence of the chiral catalyst was activated through 1,5-coordination of two carbonyl oxygen atoms of ester to copper(II), and the Re face of 3-methylindole was attacked leading to satisfactory formation of the product with S configuration 176 ab [87].

In the following, it was explored the generality of 3-functionalized indole and nitroalkene. Various nitrostyrenes having different groups on the aromatic ring have been treated with 3-methylindole 4a to provide the desired products in high yields and ees. In addition, the identical satisfactory consequences have been provided for 1-naphthyl and 2-thienyl nitroalkene derivatives. Noticeably, the transformation between a cinnamaldehyde-obtained nitroalkene substrate 89k occurred easily to give the product 179ak in 72% yield and 90% enantioselectivity. The substituent influence of 3-functionalized indole has been tested. Moderate outcomes have been detected for the transformations of 3-ethyl and 3-phenyl indole derivatives (4b and 4e) and nitrostyrene 89a, while the chemical yield for product 179ea was marginally poorer. Besides, indoles containing other groups at the C5–C7 position 4f, 4h, 4i have been examined, and the reactions with 89a provided the desired products 179fa, 179ha, and 179ia in high yields and ees. The absolute configuration of product 89ae was identified to be R on the basis of the X-ray diffraction of its single-crystal structure (Scheme 55, Table 31) [87].
2.4. Zinc

An efficient useful and high yield method for the construction of bis(indolyl)methanes (BIMs) via F-CA reaction of indoles and imine derivatives using dithiocarbhydrozone Schiff base/ligand 181/ Zn(ClO₄)₂·6H₂O as an extremely stable, significant and easily accessible catalyst was demonstrated. Moderate to good yields (up to 99%) have been provided using both substrates for imines [88]. Relied on the optimization results, different imine derivatives have been treated with indole derivatives. Initially, aromatic groups have been applied as R2. In all reactions, excellent yields have been treated with indole derivatives. Initially, aromatic groups have been provided, from 86% yield for the para-methoxy compound to 99% yield for the p-Br functionalized substrate, excepting p-N(CH₃)₂ and o-OH compounds (18% and 52% yield). Once R² was a heteroaromatic group, high yields have been detected even if the electron-withdrawing or -donating substituents were at the phenyl ring of R¹. Compared to the other groups of R², the hydridoxime imine derivatives afforded extremely poor yields (Scheme 56, Table 32) [88].

The chiral Lewis acid-mediated AF-CA of pyrrole derivatives with β-CF₃ acrylates produced different kinds of chiral trifluoromethylated compounds in high yields with excellent enantioselectivity. The F–C reaction was employed for the formation of optically active trifluorinated heliotridane [89]. Based on optimal conditions, different pyrrole derivatives have been surveyed by using 183 as the nucleophile acceptor. The transformation of unmasked pyrrole 7b afforded the corresponding product 185b in 97% chemical yield with 99% enantioselectivity. The absolute configuration of 185b has been allocated as S. Noticeably, excellent enantioselectivities have been detected regardless of the groups nature on the pyrrole nitrogen as well as the 2-position (92–97% enantioselectivity). Furthermore, pyrrole derivatives including electron-withdrawing and sterically hindered substituents for instance Bn and Ph presented lesser reactivity and selectivity (<90% enantioselectivity), usually requiring an increased reaction temperature for the reactions to attain completion. Moreover, disubstituted pyrrole derivatives 7k–m gave the corresponding products 185k–m in up to 94% enantioselectivity (Scheme 57, Table 33) [89].

Then, the AF-CA of 183 with indole and 4,7-dihydroidole were performed. While the focus of nucleophilicity of pyrrole derivatives is at C-2, it resides at C-3 for the indole derivatives. Af-CA of indole derivatives using dithiocarbohydrazone Schiff base/ligand 181/ Zn(ClO₄)₂·6H₂O as an extremely stable, significant and easily accessible catalyst was demonstrated. Moderate to good yields (up to 99%) have been provided using both substrates for imines [88]. Relied on the optimization results, different imine derivatives have been treated with indole derivatives. Initially, aromatic groups have been applied as R2. In all reactions, excellent yields have been treated with indole derivatives. Initially, aromatic groups have been provided, from 86% yield for the para-methoxy compound to 99% yield for the p-Br functionalized substrate, excepting p-N(CH₃)₂ and o-OH compounds (18% and 52% yield). Once R² was a heteroaromatic group, high yields have been detected even if the electron-withdrawing or -donating substituents were at the phenyl ring of R¹. Compared to the other groups of R², the hydridoxime imine derivatives afforded extremely poor yields (Scheme 56, Table 32) [88].

![Scheme 56. The F–C reaction of indoles and various imines.](image)

![Scheme 57. AF-C reaction of β-CF₃ acrylates 183 and pyrrole derivatives.](image)
4n (2 equiv.) proceeded smoothly supplying the 3-functionalized indole with high levels of selectivity (99% ee) and in approximately quantitative chemical yield (Scheme 58, eq. 1). However, C-2 functionalized indole derivatives were rather difficult to be synthesized via F-CA reaction. This problem was circumvented by the application of pyrrole derivative 4o as follows: the 4,7-dihydroindole 4o has been used as a disubstituted pyrrole nucleophile and readily aromatized using p-benzoquinone (p-BQ) as an oxidant [90]. Taking benefit of this property, 2-functionalized indole 188 has been effectively provided with 75% enantioselectivity in 90% yield (Scheme 58, eq. 2) [91].

An extremely AF-CA of indole derivatives and ethyl trifluoropyruvate was achieved by using N,N'-dioxide-zinc(II) systems [92]. Both enantiomers of the corresponding adducts have been provided using enantiomeric ligands in high results (up to 99% yield and 98% enantioselectivity) [93]. Under the optimum reaction conditions, both enantiomers of the corresponding products have been provided with good to high enantioselectivities. The enantioselectivity of F-CA of different indole derivatives and ethyl trifluoropyruvate has been known to be sensitive to the electronic property of the indole. Usually, indole derivatives including electron-withdrawing substituents on the phenyl ring afforded higher ee than those with electron-donating substituents. The 5-chloro indole 4j afforded the greatest yield and enantioselectivity. Once the 5-position of indole has been functionalized with a nitro substituent, 93% enantioselectivity with 66% yield has been provided. Although, a group at the 1- or 2-position of the indole ring afforded low ees. Once the group at the 1-position was Me or benzyl, the enantioselectivity of the product reduced to 46% and 56% enantioselectivity, respectively. However, the indole with a Me substituent on the 2-position acted well with ethyl trifluoropyruvate, merely 14% enantioselectivity has been provided. Meanwhile, the opposite configured products have been readily provided in moderate ees and yields by employing the 189-Zn(OTf)2 catalytic system (Scheme 59, Table 34).

Table 33
AF-CA reaction of β-CF₃ acrylates 183 and pyrrole derivatives.

| Entry | R¹, R² | Yield (%) | ee (%) |
|-------|--------|-----------|--------|
| 1     | H, H (7b) | 97 (185b) | 99     |
| 2     | H, Me (7c) | 96 (185c) | 97     |
| 3     | H, Et (7d) | 98 (185d) | 92     |
| 4     | Et, H (7e) | 96 (185e) | 96     |
| 5     | iPr, H (7f) | 96 (185f) | 95     |
| 6     | nBu, H (7g) | 95 (185g) | 93     |
| 7     | allyl, H (7h) | 90 (185h) | 95     |
| 8     | Bn, H (7i) | 93 (185i) | 85     |
| 9     | Ph, H (7j) | 94 (185j) | 88     |
| 10    | Me, Me (7k) | 97 (185k) | 94     |
| 11    | Me, Et (7l) | 99 (185l) | 88     |
| 12    | Me, Bn (7m) | 95 (185m) | 76     |

Table 34
F-CA of indole derivatives and ethyl trifluoropyruvate by N,N'-dioxide-zinc(II) systems.

| Entry | R¹ | Ligand | Yield (%) | ee (%) |
|-------|----|--------|-----------|--------|
| 1     | H  | 189a   | 97 (190a) | 90 (R) |
| 2     | 5-Me | 189a | 98 (190b) | 74     |
| 3     | 6-Me | 189a | 93 (190c) | 74     |
| 4     | 7-Me | 189a | 97 (190d) | 94     |
| 5     | 7-Et | 189b | 99 (191d) | 95     |
| 6     | 4-MeO | 189b | 96 (191e) | 94     |
| 7     | 5-MeO | 189a | 98 (190g) | 71     |
| 8     | 6-MeO | 189a | 97 (190h) | 83     |
| 9     | 5-F | 189a | 99 (191i) | 93     |
| 10    | 5-Cl | 189a | 99 (190j) | 98     |
| 11    | 5-Br | 189b | 97 (190k) | 96     |
| 12    | 5-O₂N | 189a | 66 (190) | 93     |

Scheme 58. AF-C reaction of β-CF₃ acrylates 183 and indoles.
A possible model for the transition state of AF-C reaction has been displayed in Fig. 12. The N-oxides and amide oxygens of 189d were linked to zinc (II) in a tetradentate method to provide six-membered chelate rings. In the meantime, bidentate ethyl trifluoropyruvate was linked to zinc (II) from the suitable side in this transition state, the $R_\text{e}$ face of the carbonyl substituent to the trifluoromethyl substituent was protected using the bulky 1-adamantyl substituent, permitting nucleophilic attack of indole principally, takes place from the $S_\text{f}$ face, therefore providing the $R$-configured product [93].

Diverse bis(oxazoline) ligands including gem-disubstitution on one of the oxazoline rings have been formed from ($S$)-valine. These ligands were planned as a cost-effective alternative to analogous ligands bearing an oxazolyl C(5)-tert-butyl substituent obtained from ($S$)-tert-leucine. Several of these ligands contain a C(4)-gem-dimethyl substituent and the other a C(4)-gem-diphenyl substituent linked to the C(5)-isopropyl group. Zn systems of ligand, 193 along with non-C(4)-gem-disubstituted analogues were effective in the F-CA of both indole (up to 74% enantioselectivity) and 2-methoxyfuran (up to 95% enantioselectivity) with numerous nitroalkene derivatives (Scheme 60) [94].

It was thought worthwhile to select the optimal gem-disubstituted ligand, 193, and explore a substrate scope in the AF-CA reaction of 2-methoxyfuran 196 and various nitroalkene derivatives 89. The $ee$ values obtained for the products were found being in the range of 89—95% and chemical yields of 70—85%. Under optimal reaction conditions meta-chloro-functionalized nitrostyrene, afforded alkyalted furan 198g in 95% enantioselectivity while heteroaromatic nitroalkene derivatives 89e-f afforded marginally lower yields but similar enantioselectivities (Scheme 61, Table 35) [94].

In the proposed transition states for the F-CA of indole 4 and 2-methoxyfuran 196, the two oxazolinyl nitrogen atoms are coordinated to the Zn center and the nitro group of the nitroalkene coordinates through the two oxygen atoms to the Lewis acid center. This activates the nitroalkene to nucleophilic attack by the electron-rich arene. The attack occurs preferentially at the $S_\text{f}$ face due to the influence of the substituents on each of the oxazoline rings, therefore providing an enantioenriched product with the ($R$)-configuration in the case of indole 4 and ($S$)-configuration in the case of 2-methoxyfuran 196 (Scheme 62) [94].

The AF-C amidoalkylation reactions of aryl aldimine derivatives and indoles were significantly mediated by Trost’s bis-ProPhenol dinuclear Zn systems [95] to provide 3-indolyl methanamines in moderate to high chemical yields with satisfactory to excellent $ee$ (from 70:30 up to 95: 5 $er$) [86]. Substrates 122b-g containing electron-withdrawing and donating groups at the $para$-position on the aromatic group provided the corresponding products 202b-g in moderate to high yields, although accompanied with changing values of enantiomeric ratios. Among these, the substrate 122g containing a $para$-CF$_3$ group afforded the corresponding product 202g in 98% yield with 94: 6 $er$. For substrates 122h-m containing ortho- and meta-groups on the aromatic substituent, the corresponding products 202h-m were provided in 92—98% chemical yields however with the changing values of $ee$ ranging from 76: 24 to 92: 8. Remarkably, compound 122n comprising 2,4-dichloro substituents afforded the corresponding product 202n in 98%
chemical yield with 95:5 er. Moreover, compounds 122o-q including naphthyl and thiophen-2-yl substituents were appropriate for this conversion to provide the anticipated products 202o-q in excellent yields and satisfactory ees. In addition, indoles 4b-c having 5-Me and 5-Br substituents produced the desired products 202r-s in excellent yields and satisfactory er (72:28 and 70:30) (Scheme 63, Table 36) [96].

Chiral Ph-dbfox (Ph-dbfox=(R,R)-4,6-dibenzo[2,2']-bis(4-phenyloxazoline))] [97] /Zn(NTF₂)₂ mediated AF-C reactions of β-C₅F₅ acrylates and pyrrole derivatives or indole derivatives gave the desired chiral trifluoromethyl pyrrole and indoles in excellent yields with a wide range of 66–99% enantioselectivity [98]. Using the chiral adduct of the AF-C reaction, the chiral trifluoromethylated heliotridane was effectively formed in moderate yield. The AF-C reaction of nitrogen-hydrogen pyrrole 7b and 183 gave (S)-204b in 96% yield and 98% enantioselectivity. The enantioselectivity might be more increased to 99% at 55 °C. Different protected substituents on the pyrrole nitrogen were found quite acceptable. A decrease in enantioselectivity was detected by increase in the length of the N-alkyl group of the pyrrole, perhaps due to an increase in steric influence of the shielding group. Pyrrole 7e reacted with similar enantioselectivity with pyrrole 7f due to the same steric hindrance, they experience. Moreover, the existence of electron-withdrawing and excellent steric hindrance substituents on the pyrrole nitrogen led to a reduction in enantioselectivity and yields (Scheme 64, Table 37) [98].

A probable mechanism for the AF-C reaction of pyrroles and compound 183 was shown in Scheme 65. The addition reaction of a pyrrole nucleophile to a β-trifluoromethylated α,β-unsaturated carbonyl compound 205, proceeded smoothly by asymmetric protection of the resultant transient enolate 206 to create the corresponding product 204b and the recovery of the chiral catalyst. To explain the stereochemistry of the AF-CA reaction, a probable transition-state model was presented. The acrylate links in a bidentate approach to the catalyst metal center that accepts a six-member-planar geometry and the nucleophilic pyrrole approach- tion the lower protected Re face of the olefin β-carbon resulting in the production of the main stereoisomer [98].

The catalytic AF-C reaction of indoles and 2-propargyloxy-β-nitrostyrenes and nitrodiene has been thoroughly examined in the presence of diphenylamine-linked bis-oxazoline-zinc trifluoromethanesulfonate systems [99]. Satisfactory to good ees have been provided using both types of substrates (up to 89% enantioselectivity for nitrodienes and up to 93% enantioselectivity for β-
Additional conversion of the desired F-CA product of indole and 2-propargyloxy-β-nitrostyrene has been occurred to provide the chiral isoxazolobenzoxepane derivative that is of medicinal chemistry attention, with retained enantioergic purity. Indole derivatives containing various groups have been tested in the AF-CA reaction with nitrodiene. The existence of an electron-withdrawing group like Cl in the 5-position of the indole ring in 4b provided a reasonable decline in ee, however the chemical yield was preserved. Once electron-rich 5-MeO-indole 4d has been applied, the chemical yield of the product was increased to 91%, whereas the enantioselectivity reduced marginally. Once N-methylindole has been employed, the enantioselectivity reduced compared with the formerly reported outcome.

Next, various nitrodiene derivatives have been tested in the reaction with indole 4a. In the case of methyl-functionalized nitrodiene 208b, both chemical yield and enantioselectivity reduced, maybe because of electronic and steric effects. By using Br-functionalized substrate 208c, the chemical yield of product 210g was provided with satisfactory yield and enantioselectivity. Nitrodiene derivatives having an electron-donating substituent like OMe at the para position of the phenyl ring afforded satisfactory enantioselectivity.

Due to the low solubility in the case of para-nitro-functionalized substrate 208f, both the chemical yield and enantioselectivity were poor. Due to electronic influences, 4-F-functionalized nitrodiene 208d afforded the best result; in this occasion, the desired product 210h has been provided in 75% yield and 89% enantioselectivity. It was known that the inadequate steric interaction of PhCH¼CH and the ligand decreases the enantioselectivity in comparison with that of 1-[4(4-nitrobut-3-enyl)benzene (Scheme 66, Table 38).

In the following, under the optimal reaction conditions, it was examined the substrate generality for the current reaction. The reaction time was prolonged to 48 h, since the transformations were poor with several substrates at 0 °C. All compounds treated easily to give the corresponding products with moderate to high yields. An electronic influence on the enantioselectivity has been detected. Once electron-withdrawing chlorine was existent at the 5-position of indole, both the enantioselectivity and the chemical yield reduced. In spite of the steric limitation, the existence of an electron-rich group like a MeO or EtO substituent in the aromatic ring provided a satisfactory reduction of both the enantioselectivity and chemical yield. Once a substrate containing two sterically bulky groups like tert-butyl and bromine substituents in the aromatic ring was applied, the enantioselectivity reduced in comparison with that attained with Cl-functionalized substrates.

### Table 37

| Entry | R¹, R² | Yield (%) | ee (%) |
|-------|--------|-----------|--------|
| 1     | Me, H (7a) | 96 (96) | 96 (98) |
| 2     | H, H (7b)  | 96 (97) | 98 (99) |
| 3     | Et, H (7c) | 97 (96) | 94 (96) |
| 4     | nPr, H (7d) | 95 (96) | 93 (95) |
| 5     | nBu, H (7e) | 95 (95) | 94 (95) |
| 6     | allyl, H (7f) | 94 (90) | 98 (99) |
| 7     | Br, H (7g) | 93 (204g) | 85 |
| 8     | Ph, H (7h) | 94 (204h) | 87 |
| 9     | H, Me (7i) | 96 (96) | 88 (97) |
| 10    | H, Et (7j) | 96 (98) | 84 (97) |
| 11    | Me, Me (7k) | 97 (97) | 87 (94) |
| 12    | Me, Et (7l) | 99 (99) | 70 (88) |
| 13    | Me, Br (7m) | 95 (95) | 66 (76) |

Scheme 65. Assumed catalytic cycle and probable model for the stereo-induction.

Scheme 66. AF-CA of indoles and nitrodienes.
used as the 2-substituent of the nitroethene, and the desired product has been produced with satisfactory enantioselectivity and high yield (Scheme 67, Table 39) [100].

A diastereo- and AF-CA of indoles and 3-nitro-2H-chromene derivatives mediated by diphenylamine-linked bis(oxazoline) and bis(thiazoline) zinc(II) systems was performed. Medicinally privileged indolyl(nitro) chromans 213 were subjected to AF-CA using indoles 4 to afford the desired products in moderate yields with excellent ees (up to 95%) [102]. Under optimal reaction conditions, the substrate scope the AF-CA reaction was examined by using various 3-nitro-2H-chromenes 213a-i containing. They were treated with indole to give a moderate to high chemical yields (61%–94%) of the expected products in moderate des. As far as the enantioselectivities concern, the functionalized group on the phenyl of 3-nitro-2H-chromene, having both electron-donating and withdrawing substituents, resulted in moderate ees, excepting for the substrate 213d, with which the product has been provided in good ee. In addition, once electron-rich 5-methyindole

4b and 5-methoxyindole 4c have been applied, the reaction advanced extremely easily with moderate yields, ees and des. Although, an electron-withdrawing group chlorine in the 5-position of the indole ring produced a good reduction in both chemical yield and selectivity, giving 215i in 68% yield, 62% enantioselectivity and 82:18 dr. When a Me group was attached to the indolic nitrogen atom, the reaction advanced smoothly, providing the desired product 215m in excellent yield, moderate de and ee (Scheme 68, Table 40) [102].

The suggested transition state model of this reaction is shown in Fig. 13. This catalyst acts as a bifunctional system, the NH—π interaction aims the indole attack from the back side [103], and the Lewis acid stimulates the chromene molecule through linking of the Zn cation having the two oxygen atoms in the nitro substituent. The hydrogen atom is directed to the back side to remove the steric repulsion of the phenyl group and incoming indole. The Lewis acid stimulates the chromene molecule through linking of the Zn cation having the two oxygen atoms in the nitro substituent. The hydrogen atom is directed to the back side to remove the steric repulsion of the phenyl group and incoming indole. The Lewis acid stimulates the chromene molecule through linking of the Zn cation having the two oxygen atoms in the nitro substituent. The hydrogen atom is directed to the back side to remove the steric repulsion of the phenyl group and incoming indole.

An extremely AF-CA of pyrrole with an extensive variety of simple nonchelating chalcones mediated by a chiral (Zn$_2$EtL)$_3$ ($L =

| Entry | R$^1$, R$^2$ | R$^3$, R$^4$ | Yield (%) | ee (%) |
|-------|-------------|-------------|-----------|--------|
| 1     | H, H        | Ph, H       | 79 (210a) | 87     |
| 2     | H, H        | Ph, H       | 76 (210b) | 56     |
| 3     | H, Me       | Ph, H       | 64 (210c) | 81     |
| 4     | H, MeO      | Ph, H       | 91 (210d) | 84     |
| 5     | Me, H       | Ph, H       | 73 (210e) | 47     |
| 6     | H, H        | Ph, Me      | 56 (210f) | 67     |
| 7     | H, H        | Ph, Br      | 23 (210g) | 85     |
| 8     | H, H        | Ph, Br      | 71 (210h) | 79     |
| 9     | H, H        | 4-FC$_2$H$_5$H | 75 (210i) | 89     |
| 10    | H, H        | 4-MeO$_2$C$_6$H$_4$H | 38 (210j) | 63     |
| 11    | H, H        | 4-O$_2$NC$_6$H$_4$H | 39 (210k) | 33     |
| 12    | H, H        | 2-O$_2$NC$_6$H$_4$H | 73 (210l) | 80     |

Scheme 67. AF-CA of indoles and nitroalkenes.

Table 38

| Entry | R$^1$, R$^2$ | R$^3$, R$^4$ | Yield (%) | ee (%) |
|-------|-------------|-------------|-----------|--------|
| 1     | H, H        | Ph, H       | 79 (210a) | 87     |
| 2     | H, H        | Ph, H       | 76 (210b) | 56     |
| 3     | H, Me       | Ph, H       | 64 (210c) | 81     |
| 4     | H, MeO      | Ph, H       | 91 (210d) | 84     |
| 5     | Me, H       | Ph, H       | 73 (210e) | 47     |
| 6     | H, H        | Ph, Me      | 56 (210f) | 67     |
| 7     | H, H        | Ph, Br      | 23 (210g) | 85     |
| 8     | H, H        | Ph, Br      | 71 (210h) | 79     |
| 9     | H, H        | 4-FC$_2$H$_5$H | 75 (210i) | 89     |
| 10    | H, H        | 4-MeO$_2$C$_6$H$_4$H | 38 (210j) | 63     |
| 11    | H, H        | 4-O$_2$NC$_6$H$_4$H | 39 (210k) | 33     |
| 12    | H, H        | 2-O$_2$NC$_6$H$_4$H | 73 (210l) | 80     |

Table 39

| Entry | R$^1$, R$^2$ | R$^3$, R$^4$ | Yield (%) | ee (%) |
|-------|-------------|-------------|-----------|--------|
| 1     | H, H        | H, H        | 98 (212a) | 81     |
| 2     | H, H        | H, H        | 89 (212b) | 65     |
| 3     | H, Me       | H, H        | 98 (212c) | 84     |
| 4     | H, MeO      | H, H        | 95 (212d) | 84     |
| 5     | Me, H       | H, H        | 98 (212e) | 74     |
| 6     | H, H        | H, Cl       | 79 (212f) | 90     |
| 7     | H, H        | H, Br       | 93 (212g) | 90 (%) |
| 8     | H, H        | O$_2$N      | 99 (212h) | 93     |
| 9     | H, H        | MeO         | 92 (212i) | 68     |
| 10    | H, H        | EtO         | 91 (212j) | 67     |
| 11    | H, H        | Cl, Cl      | 91 (212k) | 89     |
| 12    | H, H        | Br, Br      | 85 (212l) | 64     |
| 13    | H, H        | PhF, PhF    | 81 (212m) | 36     |
| 14    | H, H        | H, H        | 99 (212n) | 82     |

Table 40

| Entry | R$^1$ | R$^2$ | R$^3$ | Yield (%) | Anti/syn | ee (%) |
|-------|-------|-------|-------|-----------|----------|--------|
| 1     | H     | H     | H     | 80 (215a) | 89:11    | 94     |
| 2     | 6-Cl  | H     | H     | 80 (215b) | 88:12    | 83     |
| 3     | 6-Br  | H     | H     | 94 (215c) | 84:16    | 86     |
| 4     | 6-O$_2$N | H     | H     | 80 (215d) | 90:10    | 54     |
| 5     | 8-MeO | H     | H     | 84 (215e) | 89:11    | 89     |
| 6     | 8-EtO | H     | H     | 92 (215f) | 92:8     | 88     |
| 7     | 5,6-benzo | H    | H     | 61 (215g) | 95:5     | 88     |
| 8     | 6,8-Cl$_2$ | H    | H     | 90 (215h) | 90:10    | 83     |
| 9     | 6,8-Br$_2$ | H    | H     | 90 (215i) | 92:8     | 87     |
| 10    | H     | MeO   | H     | 88 (215j) | 94:6     | 92     |
| 11    | H     | Me    | H     | 92 (215k) | 91:9     | 93     |
| 12    | H     | Cl    | H     | 68 (215l) | 82:18    | 62     |
| 13    | H     | H     | Me    | 94 (215m) | 92:8     | 95     |

Scheme 68. AF-CA of indoles 4 and 3-nitro-2H-chromenes 213 catalyzed by 214-zinc trifluoromethanesulfonate.

Fig. 13. Proposed transition state of the AF-CA catalyzed by 214-Zn(OTf)$_2$ system.
(S,S)-217) system [104] was achieved. The catalyst (Zn2EtL2) system has been formed in situ by reacting the chiral ligand (S,S)-217 with 2 equiv. of diethylzinc. A number of b-pyrrrole-functionalized dihydrochalcone derivatives have been frequently provided in high yields (up to 99%) and high enantioselectivity (up to 99%) by using 15 mol % catalyst loading [105]. The absolute stereochemistry of the products has been identified to be the S-configuration by X-ray crystallographic analysis of 218g. Meanwhile, a weak undesirable nonlinear influence has been detected [105]. The generality of AF-CA reaction was tested by using different b, b-unsaturated ketone derivatives. High ees have been obtained, in spite of the electronic effect and regardless of positions of the substrates on the aromatic ring (R1). The electronic influence or positions of the substrates on the aromatic ring (R2) influenced the yields variously. The electron-donating substituent Me of the aromatic ring resulted in 99% enantioselectivity but 70% yield. The substituent on the C-5 position of indole having halogen (–Br, –Cl, –F) group at para position afforded the corresponding product with moderate ee. Naphthyl substrates treated easily with pyrrole at the optimal reaction conditions providing the corresponding products with >99% enantioselectivity. The electron-withdrawing substituents of R1 or R2 were beneficial for the reaction. Thus, substrates having two electron-withdrawing substituents occupying R1 and R2 were provided for being examined. All of them treated with pyrrole in high yields and ees. Compound 160a with a Me substituent afforded 99% enantioselectivity but 70% yield. Compounds with a strongly electron-donating substituent OMe occupying the para position of the aromatic ring R1 or R2 resulted in more system mixtures (Scheme 69, Table 41) [105].

The efficient chiral Zn(II) systems [106] have been formed and these systems exhibited the fluorescence performance. The chiral Zn(II) system has been examined in AF-CA reaction of indoles and nitroalkene derivatives [107]. In all reactions, the corresponding products have been formed with excellent yield and moderate enantioselectivity. Under optimal conditions, the AF-CA reaction of indoles and nitrostyrenes were examined. Different indole derivatives 220a-f containing various groups were reacted with nitrostyrene in moderate yields and excellent enantioselectivities. The substituent on the C-5 position of indole having halogen (–Br, –Cl) group gave moderate ees (78–76%). More, electron donating groups (–OMe, –Me) at C-5 of indole gave moderate ees. Moreover, the substituent influence on the nitrostyrene ring has been explored. The nitrostyrene having halogen (–Br, –Cl, –F) group at para position afforded desired products with moderate enantioselectivity. Electron-rich (–Me, –OMe) aromatic nitrostyrene at para position afforded the corresponding product with moderate enantioselectivity. Remarkably, a heterocyclic nitrostyrene derivative afforded moderate enantioselectivity as 220i: 72% enantioselectivity (Scheme 70, Table 42) [107].

Various chiral benzene-based tetraoxazoline ligands [108] have been synthesized in good yields via the treatment of chiral b-amino alcohols and 1,2,4,5-benzenetetracarboxylic acid through continuous elimination of H2O. The AF-CA transformation of nitroalkenes and indole derivatives has been examined by employing these new chiral catalysts, that have been produced in situ through refluxing the mentioned ligands and anhydrous ZnCl2 in solvent. Typically, high ee value (up to 98%) and good yields (up to 99%) have been developed. Based on the optimization results, this stereoselective reaction has been more considered utilizing additional nitroalkenes and indole derivatives. Initially, some indole derivatives 4a-d including diverse groups have been surveyed in the catalytic reaction. An electron-donating groups like Me or MeO in the 5-position of the indole provided a tiny improve in ee, although reduced ee value and yield have been provided for electron-deficient 5-chloroindole. Next, the scope of this alkylation

Table 41. Catalytic AF-C reaction of pyrrole 7 and chalcone derivatives 160.

| Entry | R1 | R2 | Yield (%) | ee (%) |
|-------|----|----|-----------|-------|
| 1     | Ph | Ph | 99 (218a) | 99    |
| 2     | 4-FC6H4 | Ph | 99 (218b) | 99    |
| 3     | 4-ClC6H4 | Ph | 99 (218c) | 98    |
| 4     | 4-BrC6H4 | Ph | 99 (218d) | 99    |
| 5     | 4-MeC6H4 | Ph | 94 (218e) | 98    |
| 6     | 3-ClC6H4 | Ph | 99 (218f) | 98    |
| 7     | 3-BrC6H4 | Ph | 99 (218g) | 99    |
| 8     | 2-ClC6H4 | Ph | 99 (218h) | 99    |
| 9     | Ph | 4-ClC6H4 | 99 (218i) | 98    |
| 10    | Ph | 4-BrC6H4 | 99 (218j) | 99    |
| 11    | Ph | 3-ClC6H4 | 99 (218k) | 99    |
| 12    | Ph | 3-BrC6H4 | 99 (218l) | 99    |
| 13    | Ph | 2-ClC6H4 | 99 (218m) | 99    |
| 14    | Ph | 4-MeC6H4 | 94 (218n) | 98    |
| 15    | Ph | 3-MeC6H4 | 67 (218o) | 98    |
| 16    | Ph | 2-naphthyl | 94 (218p) | >99 |
| 17    | 4-ClC6H4 | 2-ClC6H4 | 99 (218q) | 98    |
| 18    | 4-FC6H4 | 3-BrC6H4 | 99 (218r) | 99    |
| 19    | 4-BrC6H4 | 3-BrC6H4 | 99 (218s) | 99    |
| 20    | 4-FC6H4 | 4-ClC6H4 | 99 (218t) | 99    |
| 21    | 4-MeC6H4 | 4-ClC6H4 | 70 (218u) | 99    |
| 22    | 4-MeOC6H4 | Ph | – | – |
| 23    | Ph | 4-MeOC6H4 | – | – |
| 24    | Ph | Ph | n.r. | |
| 25    | Ph | Ph | 99 (218a) | 99    |

Scheme 69. Catalytic AF-C reaction of pyrrole 7 and chalcone derivatives 160.

Scheme 70. AF-CA of indole derivatives and nitroalkenes.
reaction has been more considered by using a number of structurally diverse nitroalkenes. The ortho-groups on the aromatic ring in nitrostyrenes, both electron-donating or electron-withdrawing substituted reduced the ee of the corresponding products, maybe because of the steric influence of ortho-substitutes. Satisfactory chemical yields and excellent ee might be provided for the nitrostyrenes having both electron-donating and electron-withdrawing substituted on the para or meta positions of the aromatic ring and nitroalkenes with aliphatic groups. The nitroalkene having furan provided 83% ee and 89% yield (Scheme 71, Table 43) [109].

Asymmetric AF-CA addition of indoles and βγ-unsaturated α-ketoesters mediated by utilization new chiral C2-symmetric squaramide-attached bisoxazoline-Zn(OTf)2 systems [110] have been examined. The expected indole ketoesters have been provided in excellent ee (up to 94%) and moderate to high yields (up to 98%), that is the major result on the application of chiral squaramide-linked bisoxazoline SQBOX in a catalytic asymmetric AF-CA addition. Based on the optimized results, the substrate generality of the stereoselective AF-CA addition of βγ-unsaturated α-ketoesters and indoles has been more explored. Initially, a variety of βγ-unsaturated α-ketoesters containing various groups in the aromatic ring was surveyed. All of these derivatives treated with the indole and provided the desired adducts 224 in good to excellent ee value (71–94%) and moderate to high yields (74–98%). The electronic and steric nature of the groups in the aromatic ring of the βγ-unsaturated α-ketoesters, only somewhat affected the ee value and yields. The strong electron-withdrawing group like nitro afforded a lesser ee and yield. Then, the generality of this alkylation reaction has been more revealed by changing the substituted in indoles. Once different indole derivatives containing both electron-withdrawing and electron-releasing groups at the 5-position have been applied, the alkylation advanced easily and provided the expected adducts 224 in moderate yields and excellent ee. Although, while N–Me indole has been utilized, the ee reduced to 32% enantioselectivity. Ranging the substrates to ester substituted, the desired alkylation transformation also accomplished well and afforded the alkylation adducts 224 in excellent ee value and yields [Scheme 72, Table 44] [111].

As a control test, (2S)-2-methyl-1-[(4S)-4-phenyl-4,5-dihydrooxazol-2-yl]propylamine 223 has been applied as the ligand in the typical reaction based on the optimized reaction condition; 223-Zn(OTf)2 systems generated the desired adduct in 20% enantioselectivity and 37% yield. This finding exhibits that the squaramide linker was critical for producing a synergistic catalytic influence. A provisional transition state model was suggested to clarify the detected stereochemical result. The βγ-unsaturated α-ketoester directs to the Zn center in a nearly tetrahedral geometry in the 223-Zn(OTf)2 system, and the indole attacks the βγ-unsaturated α-ketoesters preferably from the Si face, providing principal synthesis

**Table 42**

| Entry | R1 | R2 | Yield (%) | ee (%) |
|-------|----|----|-----------|--------|
| 1     | H  | Ph | 92 (220a) | 76     |
| 2     | Br | Ph | 85 (220b) | 78     |
| 3     | Cl | Ph | 87 (220c) | 75     |
| 4     | F  | Ph | 91 (220d) | 74     |
| 5     | MeO| Ph | 90 (220e) | 70     |
| 6     | Me | Ph | 89 (220f) | 76     |
| 7     | H  | 4-BrC6H4 | 87 (220g) | 69    |
| 8     | H  | 4-ClC6H4 | 91 (220h) | 76     |
| 9     | H  | 4-FC6H4  | 93 (220i) | 76     |
| 10    | H  | 4-MeC6H4 | 88 (220j) | 70     |
| 11    | H  | 4-MeOCH2C6H4 | 85 (220k) | 72     |
| 12    | H  |     | 94 (220l) | 72     |

**Scheme 71. AF-CA of indole derivatives and nitroalkenes.**

**Table 43**

| Entry | R1 | R2 | Yield (%) | ee (%) |
|-------|----|----|-----------|--------|
| 1     | H  | Ph | 98 (222a) | 95     |
| 2     | Me | Ph | 96 (222b) | 97     |
| 3     | MeO| Ph | 95 (222c) | 98     |
| 4     | Cl | Ph | 89 (222d) | 82     |
| 5     | H  | 2-MeOCH2C6H4 | 98 (222e) | 78     |
| 6     | H  | 2-CIC6H5  | 85 (222f) | 75     |
| 7     | H  | 3-BrC6H3 | 87 (222g) | 96     |
| 8     | H  | 3-OC6H4         | 95 (222h) | 94     |
| 9     | H  | 4-MeOCH2C6H4 | 91 (222i) | 90     |
| 10    | H  | 4-CIC6H4 | 94 (222j) | 95     |
| 11    | H  | 2-furyl | 89 (222k) | 83     |
| 12    | H  | Me(CH2)3 | 91 (222l) | 92     |

**Scheme 72. AF-CA addition of indoles and βγ-unsaturated α-ketoesters.**

**Table 44**

| Entry | R1, R2 | R1 | Yield (%) | ee (%) |
|-------|--------|----|-----------|--------|
| 1     | H, H   | Ph, Me (13a) | 89 (224a) | 93     |
| 2     | H, H   | 4-ClC6H4, Me (13b) | 98 (224b) | 88     |
| 3     | H, H   | 4-BrC6H4, Me (13c) | 82 (224c) | 81     |
| 4     | H, H   | 4-FC6H4, Me (13d) | 92 (224d) | 89     |
| 5     | H, H   | 4-MeOCH2C6H4, Me (13e) | 86 (224e) | 89     |
| 6     | H, H   | 4-MeC6H4, Me (13f) | 98 (224f) | 91     |
| 7     | H, H   | 4-OC6H4, Me (13g) | 83 (224g) | 79     |
| 8     | H, H   | 2-OC6H4, Me (13h) | 74 (224h) | 71     |
| 9     | H, H   | 3,4-(MeO)2C6H3, Me (13i) | 92 (224i) | 89     |
| 10    | H, H   | Ph, Me (13a) | 87 (224a) | 88     |
| 11    | S-Me   | Ph, Me (13a) | 86 (224k) | 91     |
| 12    | S-Cl   | Ph, Me (13a) | 87 (224l) | 83     |
| 13    | S-MeO  | Ph, Me (13a) | 87 (224n) | 94     |
| 14    | H, H   | Ph, Et (13j) | 83 (224n) | 89     |
| 15    | H, H   | Ph, Bn (13k) | 84 (224o) | 85     |
| 16    | H, H   | Ph, iPr (13l) | 81 (224p) | 86     |
| 17    | H, H   | Ph, vinyl (13m) | 86 (224q) | 89     |
of the (S)-configured product. The excellent ee value provided due to the well-distinct squaramide-bisoxazoline chiral environment around the Zn center (Fig. 14) [111].

The catalytic stereoselective AF-CA of trans-β-nitroolefins and indole was reported using Zn(II)-oxazoline-imidazoline catalysts. The treatment produced nitroalkylated indoles in high ee (up to 99%) and yields (up to 95%) [112]. The substrates of the treatment can be substituted aromatic nitroolefins. The greater yield and ee of the treatment might be because of the activation and stereoselective induction of chiral Lewis acids linked by the nitroolefin via a 1,3-metal linked intermediate. Lastly, employing of 10 mol % 226-Zn(OTf)2 in toluene as solvent to catalyze the treatment, was the most applied case for the AF-C reaction. To examine the generality of this reaction, indole 4 has been treated with different trans-β-nitroalkenenes 89b-i. Various samples have been took place applying ligand 226 and Zn(OTf)2 in toluene. As demonstrated in Table 45, nitroalkenenes 89 treated well with indole 4 and the expected F-C alkylated adducts 227 have been provided in poor to moderate yields (39–89%) and high ee value (95–99%). The stereoselectivity in all cases appeared to be consistent with the highest being 98.8% enantioselectivity. The treatment of nitroalkenenes having an electron-donating substituent on the aromatic ring had a greater reaction rate than the treatments of nitrostyrenes having an electron-deficient substituent. While the greater ee of the corresponding products suggested that the electron-withdrawing substituents such as F and Cl resulted in diminishing the bulkiness of groups. Indole derivatives having electron-withdrawing substituents such as F and Cl, the indole derivatives treated gradually with imine 232 and modest enantioselectivity have been provided. For 5- and 6-functionalized indole derivatives, enantiomeric purity could be increased by electron-withdrawing substituents such as F and Cl, which raised to product formation site was examined, the reaction proceeded smoothly, giving raise to product 234i in satisfactory yield and good enantioselectivity. However, when indole derivatives bearing functional groups next to nitrogen atom were reacted, the reactions proceeded slowly giving the products with low ee (Scheme 75, Table 46) [114].

A probable mechanism for the 226-Zn(OTf)2 mediated AF-CA transformation of nitroalkene and indoles was suggested in Scheme 74. The nitroalkene has been motivated via chelating to 226-zinc (II) to make a four-membered intermediate 229, that endures a nucleophilic addition reaction of indole (from the available Si face) [113] to give the AF-CA product 230. Then, H-transfer 231 followed by fragmentation, generating an adduct along with recreation of the oxazoline-imidazole-Zn(II) catalyst 228 [112].

A direct AF-CA reaction of various indole derivatives and ethyl 2-(4-methoxyphenyl)imino)acetate mediated by Trost’s dinuclear system was described in 2016 by Wang and co-workers [114]. Different 3-indolylglycines have been formed in high enantioselectivity with 10 mol% catalyst loading. The functionalized groups of indole derivatives exhibited a significant role in controlling the reaction activity and ee. Most of indoles having various substituents provided the desired products in satisfactory yield and excellent enantioselectivity. Numerous 4-functionalized indoles were examined for asymmetric construction of 3-indoleglycine derivatives. Among them, the greatest outcome was achieved when 4-bromoindole was used since the corresponding product was obtained in satisfactory chemical yield and excellent enantioselectivity (>99%). 4-Functionalized compounds having electron-rich substituents gave products in 63–72% chemical yields with high ees. Using electron-withdrawing substituents such as F and Cl, the indole derivatives treated gradually with imine 232 and modest enantioselectivity have been provided. For 5- and 6-functionalized indole derivatives, enantioselectivity could be increased by diminishing the bulkiness of groups. Indole derivatives having electron-withdrawing substituents such as F and Cl resulted in expected products with moderate enantioselectivity. Electron-rich indole derivatives treated quicker with imine 232, and 3-indolylglycines have been produced in satisfactory yields. 5-Nitro functionalized indole 4i gave the corresponding product 234i in 81% yield. This result could not be justified by electron effects. The outcome revealed that the rate of the determining step for this dinuclear Zn catalytic enantioselective reaction can be changed once the used substrate bears strong electron-withdrawing substituent. When indole 4t bearing methyl group, close to the reaction site was examined, the reaction proceeded smoothly, giving rise to product 234t in satisfactory yield and good enantioselectivity. However, when indole derivatives bearing functional groups next to nitrogen atom were reacted, the reactions proceeded slowly giving the products with low ees (Scheme 75, Table 46) [114].

A probable mechanism for this F-CA reaction was suggested by X-ray analysis of ProPhenol-Zn complex, dinuclear Zn mediated AF-C reactions by Ding and co-workers [105]. Accordingly, one equivalent of ethane is liberated by deprotonation of indole to generate intermediate 236. Ethyl glyoxylate imine 232 was stimulated upon coordination to the other Zn, leading to the creation of intermediate 237. Indole attacks favorably from Si-face of the C=N bond of imine, generating the desired intermediate 238. A proton transfer
An extremely AF-CA reaction of activated phenol derivatives with (E)-4-oxo-4-arylbutenoate derivatives was achieved using the N,N'-dioxide-Sc (III) system as the catalyst. Numerous (E)-4-oxo-4-arylbutenoate derivatives have been known to be appropriate compounds for the reaction \[115\]. The corresponding products have been produced in good to excellent yields and high ee's. Under the optimal conditions, various (E)-4-oxo-4-arylbutenoates has been examined in the AF-CA reaction with phenol. Regardless of the steric and electronic nature, or the position of the groups on the phenyl ring of the AF-CA advanced smoothly to completion. The corresponding products have been produced in excellent yields and enantioselectivity. It should be mentioned that the 3,4-dimethoxy-functionalized (E)-ethyl 4-oxo-4-arylbutenoate \[239j\] gave high ee.

### 2.5. Scandium

Varied, the reactions were performed easily with moderate ees and yields for methoxy-, ethoxy-, and isopropoxy-functionalized phenol derivatives. Next, different functionalized (E)-ethyl 4-oxo-4-arylbutenoate derivatives \[242\] has been examined in the AF-CA reaction with phenol \[240a\]. Regardless of the steric and electronic nature, or the position of the groups on the phenyl ring of \[242\] the AF-CA advanced smoothly to completion. The corresponding products have been produced in excellent yields and enantioselectivity. It should be mentioned that the 3,4-dimethoxy-functionalized (E)-ethyl 4-oxo-4-arylbutenoate \[239j\] gave high ee.

#### Table 46. Catalytic AF-CA of various indoles \[234\] and imine \[232\].

| Entry | R   | Yield (%) | ee (%) |
|-------|-----|-----------|--------|
| 1     | H   | 71        | 97     |
| 2     | 4-F | 68        | 66     |
| 3     | 4-Cl| 59        | 49     |
| 4     | 4-Br| 80        | >99    |
| 5     | 4-MeO| 63      | 94     |
| 6     | 4-BOC| 64     | 91     |
| 7     | 4-AcO| 72      | 91     |
| 8     | 4-Ph | 48       | 54     |
| 9     | 5-O,N| 81      | 30     |
| 10    | 5-F  | 77       | 86     |
| 11    | 5-Cl | 78       | 80     |
| 12    | 5-Br | 78       | 70     |
| 13    | 5-Me | 85       | 59     |
| 14    | 5-MeO| 83       | 76     |
| 15    | 6-F  | 72       | 85     |
| 16    | 6-Cl | 79       | 83     |
| 17    | 6-Br | 68       | 76     |
| 18    | 6-Me | 85       | 72     |
| 19    | 6-MeO| 68       | 66     |
| 20    | 2-Me | 88       | 51     |
| 21    | 7-Me | 36       | 12     |
| 22    | 7-Cl | trace    | –      |
enantioselectivity, while the yield has been marginally decreased in comparison with those of the mono-methoxy-functionalized one derivatives. Remarkably, substrates containing heteroaryl parts were found to be competent candidates for the catalytic AF-C reaction. Moreover, the absolute configuration of the product has been demonstrated to be R (Scheme 77, Table 47) [115].

| Entry | Ar       | R\(^1\) | R\(^2\) | Yield (%) | ee (%) |
|-------|----------|---------|---------|-----------|--------|
| 1     | Ph       | Et      | Me      | 95 (242a) | 93 (R) |
| 2     | Ph       | Me      | Me      | 98 (242b) | 93 (R) |
| 3     | Ph       | iPr     | Me      | 78 (242c) | 92 (R) |
| 4     | Ph       | Bu      | Me      | 87 (242d) | 95 (R) |
| 5     | Ph       | Bu      | Me      | 91 (242e) | 92 (R) |
| 6     | Ph       | Et      | Et      | 93 (242f) | 91 (R) |
| 7     | Ph       | Et      | iPr     | 92 (242g) | 93 (R) |
| 8     | 3-MeOC\(_6\)H\(_4\) | Et | Me | 92 (242h) | 94 (R) |
| 9     | 4-MeOC\(_6\)H\(_4\) | Et | Me | 97 (242i) | 92 (R) |
| 10    | 3,4-(MeO)\(_2\)C\(_6\)H\(_3\) | Et | Me | 78 (242j) | 97 (R) |
| 11    | 3-MeC\(_6\)H\(_4\) | Et | Me | 93 (242k) | 91 (R) |
| 12    | 4-MeC\(_6\)H\(_4\) | Et | Me | 84 (242l) | 90 (R) |
| 13    | 3,4-Me\(_2\)C\(_6\)H\(_3\) | Et | Me | 87 (242m) | 93 (R) |
| 14    | 2-FC\(_6\)H\(_4\) | Et | Me | 88 (242n) | 94 (R) |
| 15    | 4-FC\(_6\)H\(_4\) | Et | Me | 93 (242o) | 89 (R) |
| 16    | 4-BrC\(_6\)H\(_4\) | Et | Me | 93 (242p) | 91 (R) |
| 17    | 3-ClC\(_6\)H\(_4\) | Et | Me | 95 (242q) | 89 (R) |
| 18    | 4-ClC\(_6\)H\(_4\) | Et | Me | 90 (242r) | 90 (R) |
| 19    | 3,4-Cl\(_2\)C\(_6\)H\(_3\) | Et | Me | 98 (242s) | 92 (R) |
| 20    | 3-O\(_2\)NC\(_6\)H\(_4\) | Et | Me | 87 (242t) | 95 (R) |
| 21    | 4-O\(_2\)NC\(_6\)H\(_4\) | Et | Me | 92 (242u) | 94 (R) |
| 22    | 2-furyl   | Et      | Me      | 86 (242v) | 88 (R) |
| 23    | 2-thienyl  | Et      | Me      | 92 (242w) | 95 (R) |
| 24    | Ph       | Et      | Me      | 87 (242a) | 89 (R) |

Acid derivatives. Notably, for the first time, seven-membered \(\beta\)-carboline-like product was formed.

Considering the alkylidene malonate linked with scandium(III) triflate in a bidentate method [118], it was assumed that the size of the ester substituent of the alkylidene malonate can affect the ee value of the product. Therefore, diverse benzylidene malonates and different ester groups were examined under secured optimal reaction conditions. Steric hindrance of the ester substituents showed a great effect on the chemical yield and ee. However, diisopropyl benzylidenemalonate demonstrated a marginally upper ee. In addition the chemical yield was found very low compared with that of diethyl benzylidenemalonate (Scheme 78, Table 48) [117].

Alkylidene malonates bearing various structures have been examine reaction as a substrate in F-C reactions, affording the desired products with moderate to high enantioselectivity. The product has been simply transformed to various exciting compounds, for instance tryptamine derivatives, \(\beta\)-carboline and indolepropionic acid derivatives using N,N’-dioxide-Sc(III) system.

Scheme 77. Proposed catalytic cycle for AF-C reaction.

Scheme 78. Enantioselective AF-CA of indole derivatives and alkylidene malonates.
of condensed-ring, heterocyclic and difunctionalized arylidene malonates which gives moderate to high enantiomeric excesses. A simple model to examine the application of the catalyst was the reaction of methyl (E)-2-oxo-4-aryl-3-butenoates 239b,c and activated benzenes 250a-d. Methyl (E)-2-oxo-4-phenyl-3-butenoate 250a was accomplished with Sc(OTf)3 without a chiral ligand in the reaction of methyl (E)-2-oxo-4-phenyl-3-butenoate 239a with 250a and was signifi cantly mediated using the Sc(OTf)3 system of 4,4-diaryl-2-oxo-4-phenyl-3-butenoates and Sc(OTf)3 already suggested for other reactions [119]. The 4,4-diaryl-2-oxo-butyric acid methyl ester derivatives 251 were frequently provided in moderate yields and the high enantioselectivity [120]. Remarkably, the sense of the stereoinduction may be clarified with the same octahedral system between 239, pybox 251 and Sc(OTf)3 already suggested for other reactions including pyruvates, and mediated by the same system. The simple initial model to examine the application of the catalyst was the reaction of methyl (E)-2-oxo-4-phenyl-3-butenoates 239a with 250a and was accomplished in the presence of either scandium (III) trflate and a 3 Å molecular sieve (MS). The key variance is then only the required time for the full consumption of starting materials and completion of the reaction, monitored by TLC. The chemical yield 252aa was high and the enantiocselectivity at –50 °C and –20 °C was 97 and 99%, respectively. Relied on the optimization results, the reactions of methyl (E)-2-oxo-4-(4-bromophenyl)-3-butenoate and the 4-nitro-analogue 239bc and 250a have been accomplished in the presence of either scandium (III) [251]scandium(III) trflate]. Even if the reactions at –50 °C afford poor yields (56 and 20% for 239b and 239c, respectively), the enantiocselectivities are marginally lowered, but the yields are considerably greater [Scheme 81, Table 50] [120].

A high AF-CA of indole derivatives and pyrrole with chalcones mediated by a chiral N,N’-dioxide-scandium(III) trflate system were achieved which endured various substrates. The reaction advances in good to high yields and excellent enantiocselectivities applying 2 mol% for indole or 0.5 mol% for pyrrole catalyst loading [121]. In the meantime, a potent positive nonlinear influence was detected. To study the generality of this reaction, it was tested the treatments of different indole derivatives and chalcone 160a based on optimal reaction conditions. Indole derivatives having an electron-donating substituent were transformed into the corresponding products in excellent yields and enantioselectivity. Moreover, in the case of halogen-functionalized indole derivatives, the role catalyst was more significant. Remarkably, for several indole derivatives, moderate results were still preserved in the presence of the catalyst as low as 2 mol%. Once 1-methylindole 4k has been applied, a good outcome has been provided [Scheme 82, Table 51] [121].
In the following, pyrrole as a nucleophile was examined. Under identical reaction conditions, the corresponding product 256a has been provided in 45% yield and 90% enantioselectivity in 7 h. Noticeably, upon a minor variation of the catalyst complex, say by changing the ligand 253 to 255, the enantioselectivity of 256a improved to 92% utilizing 2 mol% 255-scandium(III) triflate.

Different chalcone derivatives having electron-withdrawing or -donating substituents on the aromatic ring were treated with pyrrole using 2 mol% 255-scandium(III) triflate under mild reaction conditions, providing the desired compounds in moderate yields.
and excellent ees. Once trans-1-phenylbut-2-en-1-one has been used, the desired 2-alkylated pyrrole 256h was provided with 74% enantioselectivity (Scheme 83, Table 52) [121].

To reach insight into the reaction mechanism, a C2-symmetric amide, compound 258, that was the precursor of the chiral N,N0-dioxide 253, has been formed (Fig. 16) [121].

Enantioselective nucleophilic addition reaction of indoles to prochiral electrophiles gave a valuable method for attaining chiral indole scaffolds, which signify a privileged group of biologically fascinating compounds (Scheme 84). α-Indoly(hydroxyl)acetate derivatives have been provided using the 260-Sc(OTf)3 as catalyst to afford the products in moderate yields after exclusion of the bisindole as side product. The reactions of indole derivatives and alkylidene malonates [122] or chalcone derivatives have been achieved easily to afford the corresponding indoles in good yields. Moreover, pyrrole itself was found a suitable substrate in Sc(OTf)3 mediated enantioselective reactions of chalcone derivatives 263 mediated enantioselective reactions of chalcone derivatives [121]. Controlled reversal of enantioselectivity by samarium(III) trifluoromethanesulfonate/AgAsF6 and N,N0-dioxides from the identical chiral source have been accomplished in the reaction of indole and β,γ-unsaturated α-ketoester derivatives (Scheme 85). This incidence has been confirmed using the various coordination capability between silver (I) and samarium (III) [123].

2.6. Silver

Lewis acids relied on Pd and Pt were extensively studied. They are known as an ideal conversion to examine the application of Pt group metal systems of enantiopure (S)–Me2-CATPHOS [124]. The catalysts have been provided spontaneously by the reaction between [MCl2(cycloocta-1,5-diene)] [125] (M = Pd, Pt) and either (S) –Me2-CATPHOS or (S)-BINAP in CH2Cl2 to prepare [MCl2(diphosphine)], that was successively transformed into the desired Lewis acid [M(diphosphine)][OTf2] via activation with two equivalents of silver trifluoromethanesulfonate. Next, the dienophile and alkene were added and the progress of this reaction was monitored using Gas chromatography (Scheme 86, Eqs. (1) and (2)) [126].

In this context, worth mentioning is the elegant report by Widenhoefer and co-workers on the intermolecular hydroamination of 1-alkenes with ureas in the presence of chiral gold(I) complexes [127]. This group presented a full account on the use of chiral gold(I) p-Lewis acids for the enantioselective synthesis of vinyl-tetrahydro-β-carbazoles and tetrahydro-β-carbolines by means of direct alkylation of indoles with allylic alcohols [128].
First, a wide range of chiral C2 symmetric phosphine ligands were considered in promoting the ring-closure of 275 in the presence of dinuclear gold complexes made from [AuCl(SMe2)]. Finally, it should be observed that preformed or in situ assembled 276-(Au2Cl2) complex furnished comparable chemical outcomes and when insoluble AgCl was removed by filtration from the reaction mixture no significant variations with respect to the best results were recorded (277a: yield = 69%, ee = 87%). The results of the F-C type reactions indicated that this complex (276(AuOTf)2) as catalyst showed a broad substrate scope to form 1-vinyl- and 4-vinyltetrahydrocarbazole derivatives in moderate yield. Especially, it exhibited tolerance toward various functional groups as substituents on the indole scaffold and the corresponding 1-vinyl-tetrahydrocarbazole derivatives 277b-i have been obtained in high to excellent enantioselectivity (80–96%) and good to high chemical yields (52–91%). Notably, the existence of a methyl substituent at the indole nitrogen prohibited the ring-closing during F-CA, maybe because of the unfavorable steric hindrance prompted by the Me substituent nearby the cyclization point (C2-site). The alkyl groups of the ester functions (for example methyl and tert-butyl 275h, i) did not considerably affect the stereochemical and chemical result, affording tetrahydrocarbazole derivatives in 85% and 92% enantioselectivity, respectively (Scheme 87, Table 53).

Fascinatingly, intramolecular cyclization of 280a, (S)-3,5-t-Bu-4-MeO-MeOBIPHEP in the presence of 276l gave synthetically valuable compound 281a (yield = 71%, ee = 80%) while (S)-xylylphaneophos 278d in the presence of 276d afforded tetrahydrocarbazoles 279 (yield = 75%, ee = 80% with 276a). In contrast, other C2-symmetric phosphine ligands (i.e. 276b and 276c) showed lower ees (Schemes 88, Table 54). Then, the generality of the reaction has been explored using different (Z)-alcohol derivatives 280b-e. Tolerance to various substituents on the indolyl ring has been successfully with enantioselectivity ranging from 70% to 80%. Furthermore, simply removable N-(1)-allyl substituent [131] has been introduced into the alcoholic precursor 280f and the desired
Table 53
Various 1-vinyl-tetrahydrocarbazoles 277 prepared by using of gold(I)-catalyzed allylic alkylation.

| Entry | R1 | R2 | Yield (%) |
|-------|----|----|-----------|
| 1     | 5-Br | H  | 60 (277a) |
| 2     | 5-Me | H  | 68 (277b) |
| 3     | 5-MeO| H  | 55 (277c) |
| 4     | 7-Me | H  | 91 (277d) |
| 5     | 5-BnO| H  | 78 (277e) |
| 6     | 5-Cl | H  | 52 (277f) |
| 7     | H    | H  | 74 (277g) |
| 8     | H    | H  | 53 (277h) |
| 9     | H    | Me | 0 (277i)  |

Table 54
Catalytic asymmetric intramolecular F-CA reactions for the synthesis of 4-vinyl tetrahydrocarbazoles 279.

| Entry | R1, R2 | Yield (%) |
|-------|--------|-----------|
| 1     | Et, H  | 79 (279a) |
| 2     | tBu, H | 80 (279b) |
| 3     | Me, H  | 87 (279c) |
| 4     | Et, MeO| 55 (279d) |
| 5     | Et, Me | 87 (279e) |

[Scheme 88. Catalytic asymmetric intramolecular F-CA reactions for the synthesis of 4-vinyl tetrahydrocarbazoles 279.]

THBC 281f has been provided in similar enantioselectivity (78%) (Scheme 89, Table 55) [130].

The treatment of indoles and ortho-alkynylaryl aldimines mediated using a silver binol-obtained phosphate [132] has been developed to give a wide range of enantioenriched 1,2-dihydroisoquinolines in satisfactory to good chemical yields and enantioselectivity. Under the optimal condition including 10 mol % of (S)-283, toluene in 40 °C, different materials have been occurred to examine the scope of this procedure. As shown in Table 56, compound 284b containing a Me substituent at 6 position afforded an enhanced ee value (63%) and similar yield (67%). By introducing two MeO substituents, compound 284c generated reduced chemical yield and ee value. Fascinatingly, compound 284d having an electron-withdrawing substituent (7-F) provided much improved ee (89%). Moreover to the phenyl substituted alkyne, the alkyl substituents, like cyclopropyl 284e and n-butyl 284f might also be well reacted with decent chemical yields but reduced ee. For nucleophile, indoles having different substituted groups containing both either electron-donating or electron-withdrawing substituents could be endured with satisfactory enantioselectivity and yields. Remarkably, N-methyl indole similarly afforded its corresponding compounds 284j in 59% ee and 41% yield (Scheme 90) [133].

Table 55
Intramolecular asymmetric allylic alkylation of 280a-f.

| Entry | L | R, R1 | Yield (%) | ee (%) |
|-------|---|-------|-----------|--------|
| 1     | L276b| H, Me | 72 (281a) | 40 (R) |
| 2     | L276c| H, Me | 50 (281b) | 56     |
| 3     | L276d| H, Me | 71 (281c) | 80     |
| 4     | (S)-L276a| H, Me | 75 (281d) | 80     |
| 5     | (S)-L276b| H, Me | 62 (281e) | 68     |
| 6     | (S)-L276c| Cl, Me | 93 (281f) | 79     |
| 7     | (S)-L276a| Me, Me | 75 (281g) | 80     |
| 8     | (S)-L276a| MeO, Me | 61 (281h) | 76     |
| 9     | (S)-L276a| H, Br | 95 (281i) | 70     |
| 10    | (S)-L276a| H, allyl | 72 (281j) | 78     |

Table 56
Ag(I)-catalyzed enantioselective synthesis of 1,2-dihydroisoquinolines.

| Entry | Product | R | Yield (%) | ee (%) |
|-------|---------|---|-----------|--------|
| 1     | R1 = H  | 73 (284a) | 56     |
| 2     | R1 = 6-Me | 67 (284b) | 63     |
| 3     | R1 = 6,7-(MeO)2 | 57 (284c) | 32     |
| 4     | R1 = 7-F | 65 (284d) | 89     |
| 5     | R2 = cyclopropyl | 95 (284e) | 54     |
| 6     | R2 = n-butyl | 80 (284f) | 10     |
| 7     | R1 = 7-Me | 55 (284g) | 43     |
| 8     | R1 = 5-MeO | 26 (284h) | 48     |
| 9     | R1 = 6-Cl | 50 (284i) | 33     |
| 10    | –       | 41 (284j) | 59     |

[Scheme 90. Ag(I)-catalyzed enantioselective synthesis of 1,2-dihydroisoquinolines.]
In 2010, Xia and co-workers [134] demonstrated a cooperative catalytic system established by the mixture of a chiral Brønsted acid and an iron salt, as $286$, for the stereoselective AF-CA of $\alpha$-aryl $\alpha'$-hydroxy enones and indoles. In addition, the existence of a silver salt (AgOTf) was essential to increase the ee. Generally, moderate to high yields (66–95%) and ee (73–91%) were detected, with the enones containing an electron-withdrawing substituent at the para position of the phenyl group being the best. In opposition to enones having heteroaromatic or alkyl substituents at the $\beta$-position, merely satisfactory ee (43–47%) was provided. Besides, a few substituted indoles were examined in this treatment providing extremely variable consequences: unsatisfactory ee has been provided with $N$-Methyl or 2-methyl indole (12–24% enantioselectivity) although with 5-bromo indole the desired product has been made in excellent yield (82%) and moderate ee (72%) (Scheme 91, Table 57) [134].

2.7. Indium

A regioselectivity switch and extremely AF-CA reaction of $N$-masked indoles 4 and $\beta,\gamma$-unsaturated $\alpha$-keto esters 239 was found with the help of a stereoselective binary acid catalyst which synergistically links indium halide and chiral phosphoric acid [135]. The critical roles of the indium halides such as indium (III) fluoride and indium (III) bromide lies in their ability to considerably improve both the yield and ee in 1,2- and 1,4-addition and the unforeseen results which a facile swap of the counter anions of in from $F$ to $Br$ or $Cl$ offers a regioselective shift between 1,2- and 1,4-additions with high regioselectivity and ee in both compounds. These findings emphasize the possible significance of counter anions in changing both stereoselectivity and chemoselectivity (Scheme 92) [136].

A number of $\beta,\gamma$-unsaturated $\alpha$-keto esters have been exposed to the transformation with $N$-methyl indole 288a and afforded the corresponding 1,2-addition compounds 290a-h in moderate yields and with up to 99% enantioselectivity. The transformations accommodated $N$-alkyl indoles containing a Me or a benzyl group, although, no reactivity has been identified with $N$-Boc-masked indoles. Furthermore, $\alpha$-keto ester 239b including an isopropyl ester substituent was an inactive substrate, and is maybe because

### Table 57

| Entry | $R^1$ | $R^2$ | $T$ (°C) | Yield (%) | ee (%) |
|-------|------|------|----------|-----------|--------|
| 1     | 4-ClPh | H | $-40$ | 83 | 90 |
| 2     | 4-MeOPh | H | $-20$ | 76 | 73 |
| 3     | 4-FClPh | H | $-40$ | 90 | 91 |
| 4     | 4-O2NPh | H | $-40$ | 68 | 84 |
| 5     | 3-CIPh | H | $-20$ | 82 | 85 |
| 6     | 2-CIPh | H | $-40$ | 75 | 69 |
| 7     | Ph | H | $-40$ | 70 | 86 |
| 8     | 2-Furan | H | $-40$ | 66 | 80 |
| 9     | PhCH2CH2 | H | $-40$ | 95 | 47 |
| 10    | 4-CIPh | 5-Br | $-20$ | 82 | 72 |
| 11    | 4-CIPh | 2-Me | $-20$ | 86 | 24 |
| 12    | 4-CIPh | $N$-Me | $-40$ | 92 | 12 |

In 2010, Xia and co-workers [134] demonstrated a cooperative catalytic system established by the mixture of a chiral Brønsted acid and an iron salt, as $286$, for the stereoselective AF-CA of $\beta$-aryl $\alpha'$-hydroxy enones and indoles. In addition, the existence of a silver salt (AgOTf) was essential to increase the ee. Generally, moderate to high yields (66–95%) and ee (73–91%) were detected, with the enones containing an electron-withdrawing substituent at the para position of the phenyl group being the best. In opposition to enones having heteroaromatic or alkyl substituents at the $\beta$-position, merely satisfactory ee (43–47%) was provided. Besides, a few substituted indoles were examined in this treatment providing extremely variable consequences: unsatisfactory ee has been provided with $N$-Methyl or 2-methyl indole (12–24% enantioselectivity) although with 5-bromo indole the desired product has been made in excellent yield (82%) and moderate ee (72%) (Scheme 91, Table 57) [134].

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A number of $\beta,\gamma$-unsaturated $\alpha$-keto esters have been exposed to the transformation with $N$-methyl indole 288a and afforded the corresponding 1,2-addition compounds 290a-h in moderate yields and with up to 99% enantioselectivity. The transformations accommodated $N$-alkyl indoles containing a Me or a benzyl group, although, no reactivity has been identified with $N$-Boc-masked indoles. Furthermore, $\alpha$-keto ester 239b including an isopropyl ester substituent was an inactive substrate, and is maybe because
of the steric hindrance of the bulky ester scaffold. Correspondingly, aliphatic β,γ-unsaturated α-keto esters have been tested in the this catalysis and afforded high ee but poor yield [137]. The application of an ethyl ester group offers only trace quantities of the corresponding product. Furthermore, the transformation did not act with γ-heteroatom-substituted keto esters like (E)-methyl-4-ethoxy-2-oxobut-3-enoate, and is maybe because of the electron-donating ethoxyl group. Generally, the 1,2-addition transformations continued simply with only trace quantities of 1,4-products being identified in all derivatives. Moreover, no bisindole compounds were detected in this reaction and most of the indole starting material was readily recycled. The usage of only 288a in the absence of InF3 usually provided lower activity and ee (Scheme 93, Table 58) [136].

Then, the generality of the 1,4-addition transformations has been surveyed by using 288b/indium(III) bromide or 288c/indium(III) bromide binary complexes. The transformation act well by a number of β,γ-unsaturated α-keto esters containing both aliphatic or γ-aromatic substituents and N-masked indoles [138]. These transformations afforded the corresponding 1,4-addition adducts in satisfactory yields and with high regio- and enantioselectivity. The transformation did not function with γ-heteroatom-substituted keto esters like (E)-methyl 4-ethoxy-2-oxobut-3-enoate. In this investigation, 288b/indium(III) bromide and 288c/indium(III) bromide accomplished similarly fine with the latter demonstrating somewhat improved ee in various cases. Fascinatingly, the application of 288b/indium(III) bromide allowed a fruitful transformation (87% yield and 93% ee; even once 288c/indium(III) bromide failed. The 288b/indium(III) bromide system also displayed enhanced ee over 288c/indium(III) bromide by using aliphatic β,γ-unsaturated α-ketoesters (Scheme 94, Table 59) [136].

### Table 58

| Entry | Product | Entry | Product |
|-------|---------|-------|---------|
| 1     | ![Image](image1.png) | 2     | ![Image](image2.png) |
| 2     | ![Image](image3.png) | 3     | ![Image](image4.png) |
| 4     | ![Image](image5.png) | 6     | ![Image](image6.png) |

### Scheme 93

Enantioselective 1,2-addition of N-protected indoles 4 and various α-keto esters 13.

### Scheme 94

Enantioselective 1,4-addition of N-protected indoles 4 and various α-keto esters 13.

### 2.8. Zirconium

Chiral systems of 1,1′-bi-2-naphthol-based ligands having Zr tert-butoxide was prepared and examined as a catalyst system in the F-CA of pyrrole derivatives and α-ketoesters to give tertiary alcohol derivatives in moderate yields and good enantioselectivity [138]. Moreover, the reaction is extended to the reaction of 4,7-dihydroindole to afford C2-alkylated indole derivatives with moderate to excellent enantioselectivity. The re-1,4-addition transformations have been recognized as the best substrates for this reaction. To establish the generality of the reaction, different functionalized α-ketoester derivatives have been recognized as the best substrates for this reaction. To establish the generality of the reaction, different functionalized α-ketoester derivatives 291g-m were reacted with pyrrole 7a. All reactions gave the desired products 293 ag-am with moderate to excellent enantioselectivity. The reaction with ethyl α-ketoester derivatives comprising weak electron-donating (−Me) or electron-withdrawing (−Cl) substituents on the phenyl ring afforded improved ee and low yields and ees than those comprising strong electron-donating such as methoxy or electron-withdrawing such as −NO2 or −Cl substituents on the phenyl ring. The presence of substituent on ortho position of the phenyl group of the ethyl α-ketoester decreased the reaction rate as well as decreasing the chemical yield of the alkylation product lowered as low as 13% (65% enantioselectivity), demonstrating the effect of steric influence caused by the substituents placed on ortho position. Furthermore, the 2-naphthyl...
Table 59
Enantioselective 1,4-addition of N-protected indoles 4 and various α-ketoesters 13.

| Entry | Product | Entry | Product |
|-------|---------|-------|---------|
| 1     | ![Product](image1) | 7     | ![Product](image2) |
| 2     | ![Product](image3) | 8     | ![Product](image4) |
| 3     | ![Product](image5) | 9     | ![Product](image6) |
| 4     | ![Product](image7) | 10    | ![Product](image8) |
| 5     | ![Product](image9) | 11    | ![Product](image10) |
| 6     | ![Product](image11) | 12    | ![Product](image12) |

α-kETOESTER 291n and heteroaromatic α-ketoester derivatives 291o and 291p can be successfully used as substrates in this reaction, providing the desired alkylated pyrrole derivatives in satisfactory yields and excellent ees. Lastly, ethyl (3,5-difluorophenyl)oxoacetate 291m, containing two additional groups on the phenyl ring, afforded the desired alkylated pyrrole 293m with a moderate yield and ee. Inappropriately, the reaction with the aliphatic α-ketoester 291l occurred with a low yield (30%) and enantioselectivity (46%). Moreover, the influences of pyrrole group have been examined. 2-Ethylpyrrole 7b and 2-(3'-oxobutyl)pyrrole 7c resulted in the C5 alkylation products with moderate chemical yields and high enantioselectivities [Scheme 95, Table 60] [138].

Fascinatingly, 4,7-dihydroindole 187, as a disubstituted pyrrole was reacted with various aromatic and heteroaromatic α-ketoester derivatives 291 to afford the C2-alkylated indole derivatives 293 with moderate chemical yields and ees upon oxidation reaction with p-benzoquinone [Scheme 96, Table 61] [139].

Remarkably, theoretical and experimental investigations on the structure of various systems relied on (R)-3,3'-Br2-BINOL ligand and substituent (IV) metals applied as catalysts in an AF-CA of indole derivatives and α,β-unsaturated ketone derivatives were explored in 2012 by Cano and co-workers [140]. NMR spectral analysis of these catalysts proposed that at ambient temperature the catalysts would provide a monomeric structure in the case of titaniumIV and a dimeric structure in the cases of zirconium(IV) and hafnium(IV). The dimeric structure with a doubly bridged scaffold serves as bridge between the metal centers (Novak’s model) is more stable than the dimeric structure with a doubly bridged

Scheme 95. AF-C reaction of pyrroles 7 and α-ketoesters 291 catalyzed by 292-Zr(O-t-Bu)4.

Table 60
AF-C reaction of pyrroles 7 and α-ketoesters 291 catalyzed by 292-Zr(O-t-Bu)4.

| Entry | R1 | R2, R3 | Yield (%) | ee (%) |
|-------|----|--------|-----------|--------|
| 1     | H  | Et     | Ph, Et (291a) | 79 (293aa) | 98 |
| 2     | H  | Me     | Ph, Me (291b) | 55 (293ab) | 97 |
| 3     | H  | Ph     | Ph, Ph (291c) | 58 (293ac) | 98 |
| 4     | H  | Ph     | Ph, Ph (291d) | 33 (293ad) | 90 |
| 5     | H  | Ph     | Ph, Ph (291e) | 49 (293ae) | 97 |
| 6     | H  | Ph     | Ph, Ph (291f) | 79 (293af) | 97 |
| 7     | H  | Me     | 4-MeC6H4, Et (291g) | 56 (293ag) | 97 |
| 8     | H  | 2-MeC6H4, Et (291h) | 13 (293ah) | 65 |
| 9     | H  | 4-MeOC6H4, Et (291i) | 35 (293ai) | 98 |
| 10    | H  | 4-ClC6H4, Et (291j) | 69 (293aj) | 96 |
| 11    | H  | NCC6H4, Et (291k) | 62 (293ak) | 91 |
| 12    | H  | 4-O2NC6H4, Et (291l) | 77 (293al) | 60 |
| 13    | H  | 3,3'-Br2-BINOL | 72 (293am) | 77 |
| 14    | H  | NCC6H4, Et (291m) | 63 (293an) | 98 |
| 15    | H  | 2-thiophenyl, Et (291n) | 68 (293ao) | 95 |
| 16    | H  | Ph       | 2-furanyl, Et (291o) | 43 (293ap) | 90 |
| 17    | H  | Ph      | Ph, CH2Cl2, Et (291p) | 30 (293aq) | 46 |
| 18    | Et | Ph      | Ph, Et (291q) | 82 (293ar) | 92 |
| 19    | Et | Ph      | Ph, Ph (291r) | 62 (293bs) | 93 |
| 20    | Et | Ph      | Ph, Ph (291s) | 67 (293bt) | 83 |
| 21    | CH3COCH2CH2 (7c) | Ph, Et (291t) | 71 (293ca) | 96 |

Scheme 96. AF-C reaction of 4,7-dihydroindole 187 and α-ketoesters 291 catalyzed by 292-(O-t-Bu)4.
Table 61
AF-C reaction of 4,7-dihydroindole 187 and s-ketoesters 291 catalyzed by 292-(O-t-Bu)₄Zr.

| Entry | R²      | Yield (%) | ee (%) |
|-------|---------|-----------|--------|
| 1     | Ph (291a)| 76 (293a) | 91     |
| 2     | 4-MeC₆H₄ (291g) | 66 (293g) | 92     |
| 3     | 4-ClC₆H₄ (291j) | 85 (293j) | 83     |
| 4     | 2-naphthyl (291a) | 74 (293a) | 90     |
| 5     | 2-thiophene-ÿ (291e) | 51 (293e) | 84     |

Scheme 97. AF-C reaction of indoles with α,β-unsaturated ketones Zr(O-t-Bu)₄.

Table 62
AF-C reaction of indoles with α,β-unsaturated ketones Zr(O-t-Bu)₄.

| Entry | Ar, R   | Yield (%) | ee (%) |
|-------|---------|-----------|--------|
| 1     | Ph, Me  | 87 (255aa)| 97     |
| 2     | Ph, Et  | 87 (255ab)| 94     |
| 3     | Ph, Pr  | 82 (255ac)| 97     |
| 4     | Ph, Ph  | 25 (255ad)| 96     |
| 5     | p-MeC₆H₄, Me | 91 (255ae) | 95     |
| 6     | m-MeC₆H₄, Me | 84 (255af)| 92     |
| 7     | o-MeC₆H₄, Me | 73 (255ag) | 72     |
| 8     | p-MeO-C₆H₄, Me | 54 (255ah)| 95     |
| 9     | p-FC₆H₄, Me | 92 (255ai) | 96     |
| 10    | p-BrC₆H₄, Me | 95 (255aj)| 97     |
| 11    | 2-naphthyl, Me | 89 (255ak)| 98     |
| 12    | 2-thienyl, Me | 87 (255al) | 96     |

Scheme 98. AF-C reaction for the synthesis of trans-dihyronaphthofurans.

Table 63
AF-C reaction for the synthesis of trans-dihyronaphthofurans.

| Entry | R       | Yield (%) | ee (%) |
|-------|---------|-----------|--------|
| 1     | Ph (297a)| 71 (299a) | 98     |
| 2     | 4-MeC₆H₄ (297b) | 85 (299b) | 94     |
| 3     | 4-ClC₆H₄ (297c) | 45 (299c) | 94     |
| 4     | 2-FC₆H₄ (297d) | 94 (299d) | 88     |
| 5     | 4-FC₆H₄ (297e) | 90 (299e) | 97     |
| 6     | 4-BrC₆H₄ (297f) | 78 (299f) | 92     |
| 7     | 4-BrC₆H₄ (297g) | 72 (299g) | 99     |
| 8     | nBu (297g) | 55 (299g) | 91     |
| 9     | (Bu) (297h) | n.r.     | –      |

2.9. Sodium

Chiral trans-dihydroarylfurans were formed in moderate yield and high enantioselectivity from the reaction of (Z)-bromonitroalkene derivatives and naphthols utilizing a squaramide catalysis [141]. The generality of this reaction was explored with various groups at the bromonitroalkene. Electron-donating substituents for instance p-methyl or p-methoxy gave products 299b and 299c with moderate ee, however in the case of the p-methoxy substituent, the provided yield was poorer because of the lower electrophilicity of the nitroalkene 297c. In addition, halogen groups, for instance ortho- or para-F Videos 299d and 299e have been provided with similar yields. An alkyl substituent for example n-butyl provided the corresponding product 299g. Although, the usage of bulkier alkyl substituents, like t-butyl was not compatible, because of the steric hindrance of the first stage. Besides, this low reactivity has been detected for non-bromonitroalkene derivatives (Scheme 98, Table 63) [142].

An extremely enantioselective addition of aldehydes to isoquinoline, improved by the Hayashi-Jørgensen [143] secondary amine catalyst, was developed in 2013 [144]. The method has an extensive scope, with CbzCl or Boc₂O applied to motivate isoquinoline to nucleophilic addition, permitting for the simple formation of valuable synthetic intermediates in excellent enanomeric excesses. The corresponding products provided are synthetic intermediates for the formation of tetrahydropyroloberberine alkaloids. This procedure was used in the first stereoselective synthesis of 13-methyl tetrahydropyroloberberine. Upon various efforts and vigilant optimization, it was identified appropriate reaction conditions for the motivation of electron rich and electron poor isoquinolines and improves the substrate generality for the AF-CA transformation. The treatment of 300a was effective with a variety of linear aliphatic aldehydes 301b,d and phenyl acetaldehyde 301h, but the existence of bulky substituents on the alkyl chain decreased the yields of the desired products. Acetaldehyde provided the expected product 303c in satisfactory enantioselectivity and poor yield (Scheme 99, Table 64) [144].

Isoquinolines containing electron withdrawing or electron donating groups on the 3,4,5,6,7- positions, with propionaldehyde 301a were examined. All compounds gave the desired products except 5-(N)-pyrrolyldinylosoquinoline 300h, maybe because of the existence of the amine functional group on this specific substrate. 6-Me-isoquinoline 300g, electron-rich isoquinolines 300d, 300f, 5-allyl isoquinoline 300e and 4-benzyl-isoquinoline 300i provided the expected compounds in moderate yields, similar to other previously procedures. Instead, 5-bromo isoquinolines 300b afforded 304b with a somewhat reduced yield, as would be anticipated relied on its poor nucleophilicity. 3-Methyl-isoquinoline 300c provided 304c in low yield maybe because of the steric hindrance at the 3-position (Scheme 100, Table 65) [144].

Bis-camphorsulfonyl urea 305 was synthesized in a single step from camphor sulfonylamine and triphtogene. To evaluate this catalyst, it was examined the AF-CA reaction of nitrostyrene and pyrrole [145]. Based on the optimal conditions described in Scheme...
nitrostyrene links the urea in this conformation, the camphor substituents are far away from the emerging chiral center. Thus, the camphor substituents are not capable to make bias of pyrrole to each face of the nitrostyrene, thus leading to low selectivity \[145\].

It was surveyed the substrate generality of this transformation using different nitroalkene derivatives. Aryl substituents having...
Furthermore, this treatment endured various groups somewhat lesser, maybe related to the steric in-
tionalized nitroalkene derivatives has been accomplished with

Table 66

| Entry | R1 | R2 | Ar       | Yield (%) |
|-------|----|----|----------|-----------|
| 1     | H  | H  | Ph       | 85        |
| 2     | H  | H  | 2-MeOC6H4 | 76        |
| 3     | H  | H  | 3-MeOC6H4 | 78        |
| 4     | H  | H  | 4-MeOC6H4 | 80        |
| 5     | H  | H  | 4-ClC6H4  | 77        |
| 6     | H  | H  | 4-BrC6H4  | 73        |
| 7     | H  | H  | Furan     | 71        |
| 8     | Me | H  | 4-O2NC6H4 | 39        |
| 9     | Me | H  | Ph        | 84        |
| 10    | Me | H  | 3-MeOC6H4 | 77        |
| 11    | Me | H  | 2-MeOC6H4 | 96        |
| 12    | Me | H  | 4-ClC6H4  | 95        |
| 13    | Me | H  | 4-MeOC6H4 | 77        |
| 14    | Me | H  | Furan     | 87        |
| 15    | Me | H  | 4-BrC6H4  | 88        |
| 16    | Me | H  | 1-naphthyl| 81        |
| 17    | H  | MeO| C6H5      | 44        |
| 18    | H  | MeO| Furan     | 53        |

Scheme 103. F–C reaction of indoles with β-nitrostyrenes catalyzed by complex 309.

2.10. Nickel

[Ni(L2)(CH3CN)][PF6]2 (305). L = 3-(1-ethyl-1H-benzimidazol-
2-yl)methyl)-1-((6-methylpyridin-2-yl)-methyl)benzimidazolylidene) was effectively synthesized in 2011 [146]. The Ni complexes
disclose a square-planar construction having two carbene ligands and benzimidazole substituents at the cis configuration. The Ni complex 305 was exhibited to be an extremely effective catalyst for AF-CA reaction of β-nitrostyrenes and indoles at ambient temper-

ature in satisfactory-to-high chemical yields. The expected indoles have been generated in satisfactory-to-high yields with up to 96%. In addition, the electronic density on the indole ring would show a significant factor in this treatment. The indole containing Me sub-
stituent at the 2-position, made the desired adducts in high yields.

In the following, 5-(methoxy)-1-
H-indole, the reactivity was somewhat lesser, maybe related to the steric influence of the MeO substituent. Furthermore, this treatment endured various groups like bromine, chlorine, MeO substituents at the aromatic ring in β-
nitrostyrenes. The β-nitrostyrene including bromine or NO2 sub-
stituents provided a lesser yield, in opposition to, the β-nitro-
styrene containing MeO substituent at the 2- and 4-position, provided the expected adducts in high chemical yields (Scheme 103, Table 66) [146].

A highly AF-CA of indole derivatives using β–CF3–β-difunctionalized nitroalkene derivatives has been accomplished with Ni(ClO4)2-bisoxazoline system [147] as a catalyst that gave indole-containing chiral compounds with trifluoromethylated all-carbon quaternary stereogenic centers in moderate chemical yields and high ees [148]. With the optimum conditions in hand, an extensive variety of nitroalkene derivatives 311a-n have been examined. The nitroalkene derivatives containing meta- or para-groups on the aromatic ring were well endured, and their transformations with indole proceeded smoothly to give the desired products in high ees. Comparatively, lower yields have been obtained for products 313ia and 313ia, displaying that the electronic effect of para-electron-withdrawing groups has an undesirable effect on the reactivity. Moreover, the yields have been affected adversely by the steric influence of the substrate. For instance, modest yields have been provided for the corresponding products 313ga, 313ha, and 313na, including 3,5-difunctionalized phenyl and 2-naphthyl substituents. Furthermore, no reaction occurred for nitroalkene 311d involving an ortho-tolyl substituent (Scheme 104, Table 67) [149].

Noticeably, a catalytic enantioselective intermolecular C2 F-CA reaction of N-methyl skatole and βγ-unsaturated α-ketoester der-
avatives was achieved with a chiral N,N'-dioxide-Ni(II) system. Based on optimal conditions, the desired indoles have been pro-
vided in moderate yield and high ees [150]. Peng and co-workers examined the alkylation reaction of N-methyl skatole 4 and βγ-
unsaturated α-ketoester 239 by using chiral Lewis acid catalysts of ligand 318. They doubtful that a dearomatization compound could
be provided from the initial C$_2$ nucleophilic addition reaction of the N-methyl skatole to the $\beta$,$\gamma$-unsaturated $\alpha$-ketoester, succeeding an iminium trapping sequence [151]. However, a formal C2 alkylation product 314 was solely produced instead of tetrahydropyrano[2,3-$b$]indole derivatives (Scheme 105) [152].

To examine the scope of the reaction, different $\beta$,$\gamma$-unsaturated $\alpha$-ketoester derivatives were exposed to the optimal conditions. Varying the ester substituent in 13 from Me to Et, benzyl, allyl, isopropyl, and tert-butyl has no noticeable influence on the reaction. Furthermore, high yields and ees were provided, in spite of the electronic effect or the position of the groups on the aromatic ring of ketoester derivatives. Fused-ring functionalized $\beta$,$\gamma$-unsaturated $\alpha$-ketoester derivatives, cinnamyl-, heteroaromatic-, and disubstituted derivatives are appropriate substrates for this reaction (64–88% chemical yields and 93–97% ee). The absolute configuration of 320b was identified to be $R$ (Scheme 106, Table 68) [150].

A catalytic model was suggested for the intermolecular C2 alkylation reaction as shown in Scheme 107. In the initial step, the tetradentate N,N’-dioxide 318 and the bidentate $\beta$,$\gamma$-unsaturated $\alpha$-ketoester 239 links with nickel(II) created an intermediate. The Si-face of the $\beta$,$\gamma$-unsaturated $\alpha$-ketoester was protected by the adjacent amide substituent of the ligand, and the N-methyl skatole 4a attacks principally from the Re-face. Considering the negative influence of bulky groups at C3- and N-positions of indole derivatives, it is assumed that a straight attack at the 2-position of indole 4a dominated in this approach, thus a C3-alkylation reaction, proceeded via migration and along with loss of a proton [152d].

A highly AF-CA reaction of indole derivatives with acyclic $\alpha$-functionalized $\beta$-nitroacrylates was achieved based on catalysis of Ni(ClO$_4$)$_2$-bisoxazoline system [153] at 1 mol % catalyst loading, giving chiral indolic $\beta$-nitroester derivatives containing all-carbon quaternary stereocenters in high yields and enantioselectivities of up to 97% [154]. The optimized conditions have been used to the reactions of numerous nitroacrylate derivatives 322a-n. As exhibited in Table 69, the chemical yields and ees are usually high for $\alpha$-aryl-$\beta$-nitroacrylate derivatives 322a-d bearing both electron-donating substituents and electron-withdrawing substituents on the aromatic ring. However, no reaction happened for $\alpha$-methyl-functionalized substrate, indicating how steric hindrance influences of on the reactivity. Moreover, heteroaryl 322j, 322k and 2-naphthyl 322l substrates treat well with indole to supply the desired products in similarly high yields and enantioselectivities. Strangely, alkylated compounds 322m and 322n were found appropriate for this conversion to give the desired products in marginally poorer yield and enantioselectivity with 5 mol % of catalyst. Noticeably, by using 0.1 mol % catalyst the transformations of substrates 322e and 322g happened easily to give the desired products in modest yields and moderate ees (Scheme 108) [154].

Chiral nickel (II)-systems of N,N’-dioxides [155] display excellent catalytic activity and enantioselectivity in mediating the AF-C C3-alkylation reaction of 2,5-dimethyl pyrrole to $\beta$,$\gamma$-unsaturated $\alpha$-ketoester derivatives [156]. A vivid reversal of ee was recognized with ligands obtained from the similar kind of chiral source of L-rampil, by marginally tuning the amide units. To examine the scope of the catalytic complexes, the substrate generality for the (+)-enantiomer of pyrrole ester derivatives 326 has been examined with L-RaPr$_2$-Ni(OTf)$_2$ system as the catalyst. Different $\beta$,$\gamma$-unsaturated $\alpha$-ketoester derivatives having 2,5-dimethylpyrrole provided the desired products with high yields and ees. Remarkably, the ester substituent had a small effect on the result. $\gamma$-Aryl
ketoester derivatives containing a halo-substituent at the ortho position undertook the reaction with relatively higher enantioselectivity than the others (up to 99% enantioselectivity). Electron-donating groups gave the corresponding products slowly in comparison with the electron-withdrawing substrates. Furthermore, naphthyl and 2-thienyl or 2-furanyl functionalized ketoester derivatives treated well with 2,5-dimethyl-pyrrole, providing the corresponding products in high enantioselectivities and good chemical yields. Particularly, an aliphatic ketoester using this catalytic complex reaction provided the desired products in 78% chemical yield and 86% enantioselectivity.

Then, Feng and co-workers advanced to make the antipodes of the adducts by the application of the L-Ra system as the catalyst, instead. The F-CA reaction with 2,5-dimethylpyrrole was tolerable to different functionalized \( \beta,\gamma \)-unsaturated \( \alpha \)-ketoester derivatives, regardless of the electron-rich or electron-deficient characteristic of the substituents. Remarkably, the enantioselectivity was fairly like to its desired enantiomer in almost all the cases. The yield was marginally higher than the desired enantiomer, for instance for 3-methoxylphenyl, 2-thienyl,
nitroalkene derivatives have been explored with excellent enantioselectivity. Lastly, the reaction of 5 mmol of [156]. Using a nickel(II) perchlorate-bisoxazoline system as a catalyst, F-CA of 4,7-dihydroindole derivatives with β−CF3−β-disubstituted nitroalkene derivatives have been explored with excellent ees to afford alkylated dihydroindole derivatives containing trifluoromethylated all-carbon quaternary stereocenters in moderate yields [157]. The desired chiral C2 alkylated indole derivatives have been produced with complete conservation of enantiomeric purity by oxidation with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ). Under optimal conditions, Jia and co-workers explored the scope of this reaction. Various functionalized nitroalkene derivatives and 4,7-dihydroindole derivatives have been examined. Both electron-donating and withdrawing groups in the para- or meta-position on the aromatic ring of nitroalkene derivatives have been well endured, and their reactions with 4,7-dihydroindole easily gave the desired products with high yields and moderate to high ees. Although, the reactivity was sharply affected by the steric influence of nitroalene, no reaction has been detected for the substrate 311m, demonstrating the restriction of this approach. Furthermore, the 3-thienyl and 2-naphthyl products 328ia and 328ja have been separated in moderate yields, however the enantioselectivity of 328ia was poorer. Moreover, modest ees have been detected in the reactions of alkylated nitroalkene derivatives 311k and 311l, however moderate yields were provided. The reaction has been effectively extended to 4,7-dihydroindole derivatives containing 5-F, 5-Me, and 6-F groups, attaining moderate yields and ees in their reactions with nitroalkene 311a (Scheme 110, Table 71) [157].

### Table 70
Substrate scope of β−γ-unsaturated α-κetoesters 13.

| Entry | R1 | R2 | Yield (%) | ee (%) |
|-------|----|----|-----------|-------|
| 1     | Ph | Me | 92 (95)   | 95 (96) |
| 2     | Ph | Et | 84 (85)   | 96 (96) |
| 3     | Ph | Bn | 89 (91)   | 95 (93) |
| 4     | Ph | Bz | 91 (91)   | 91 (93) |
| 5     | 2-ClC6H4 | Me | 89 (91) | 98 (67) |
| 6     | 2-BrC6H4 | Me | 89 (89) | 94 (60) |
| 7     | 3-ClC6H4 | Me | 93 (89) | 93 (60) |
| 8     | 4-ClC6H4 | Me | 95 (95) | 94 (93) |
| 9     | 4-O2NC6H4 | Me | 92 (89) | 88 (92) |
| 10    | 4-MeC6H4 | Me | 90 (91) | 91 (94) |
| 11    | 4-PhC6H4 | Me | 89 (91) | 91 (94) |
| 12    | 3-MeOC6H4 | Me | 88 (92) | 93 (93) |
| 13    | 4-MeOC6H4 | Me | 89 (91) | 90 (94) |
| 14    | 3,4-Cl2C6H4 | Me | 89 (92) | 93 (92) |
| 15    | 1-naphthyl | Me | 79 (80) | 93 (91) |
| 16    | 2-naphthyl | Me | 89 (89) | 93 (94) |
| 17    | 3-thiophenyl | Me | 84 (95) | 92 (93) |
| 18    | 2-furanyl | Me | 96 (95) | 92 (96) |
| 19    | c-hexyl | Me | 68 (95) | 94 (91) |

### Scheme 109.
Substrate scope of β−γ-unsaturated α-κetoesters 13.

2.11. Yttrium

A significant yttrium(III) [158]-mediated extremely AF-CA of β-trichloro(trifluoro)methyl aryl enone derivatives was demonstrated [159]. This reaction supplied numerous substituted indole derivatives with a chiral tertiary carbon center containing a trichloro(trifluoro)methyl substituent in high outcomes (up to 96% enantioselectivity and 99% yield). In this route, different β-trichloromethyl aryl enone derivatives 329 and indole derivatives 4 have been provided the corresponding products with excellent ees. Notably, both the electronic nature and the position of the groups at the aromatic ring of enone derivatives had slight effect on the enantioselectivity and reactivity (88–96% enantioselectivity, 71–99% yield). Furthermore, heteroaromatic and fused ring compounds were appropriate, providing the corresponding products with moderate outcomes. Regarding the indole ring including...
electron-donating substituents (Me or OMe), the reaction advanced easily to give trichloroalkylated indole derivatives in high yields and with up to 93% enantioselectivity. However, the halogen-functionalized indole derivatives gave good yields and ees (Scheme 111, Table 72).

Frequently, the β-trifluoromethyl aryl enone derivatives 332 displayed higher activity than β-trichloromethyl aryl enone derivatives 326. Apparently, the CF₃ substituent favors the F—C reaction because of its greater electron-withdrawing group. The desired trifluoromethylated indole derivatives have been provided in excellent yields and ees. Furthermore, once the reaction has been scaled up tenfold with 5 mol% of 330-ytterbium(III) trifluoromethanesulfonate system, high outcomes (99% yield and 94% ee) have been preserved, that highlighted the synthetic usefulness of the approach (Scheme 112, Table 73) [160].

Relied on the absolute configuration of the product 331a and preceding investigations on N,N′-dioxide-metal systems [122,161], a probable model for transition state was suggested (Fig. 18). As exhibited in Fig. 18, the oxygens of N,N′-dioxide, amide oxygens linked to yttrium (III) in a tetradentate method to make two six-membered chelate rings, and the enone 329a can link to yttrium (III) from the more available side. The incoming indole favors to attack the Re face instead of the Si face of the enone 329a since the latter is powerfully protected with the nearby 2,6-disopropylphenyl substituent of N,N’-dioxide 330, that leads to the S-configured product [159].

2.12. Dysprosium

The catalytic AF-CA of indoles and α,β-unsaturated trifluoromethyl ketone derivatives was performed by using the Dy(OTf)₃/Pybox system to afford the corresponding compounds in excellent yields and moderate ees [162]. The AF-CAs of different indoles 4 and 335 were examined in the presence of Dy(OTf)₃/Pybox 336 complex. All reactions afforded the corresponding adducts 337a-j in moderate yields. Although, N-alkylated indole derivatives had a negative influence on enantioselectivity (R² = Me and BrN). In contradiction of the electron-donating substituents that show a useful influence (R² = methoxy and methyl), the electron-withdrawing substituents (R² = Cl, F, Br, CN, CO₂Me) in C-5 of the indole scaffold seem to cause poor enantioselectivities and low reactivities. The poor reactivities were overwhelmed by the application of higher concentrations of indole derivatives in an extended reaction time to attain the corresponding products in moderate yields (Scheme 113, Table 74) [162].

2.13. Platinum

Investigations towards the synthesis and characterization of a cationic NCN pincer Pt(II) aquo system with a chiral bis[imidazo- lyl]phenyl (Phesim) ligand were described in 2012 by Song and co-workers [163]. One of the desired cationic chiral NCN pincer
enantioselectivity. A more decline in temperature (0 to 36 h, whereas the enantioselectivity was increased to 78% 338

338

a reduced yield of 84% has been provided with 5 mol % of system

resulted in an extreme drop in the yield, but with a more

pure form from the reaction of the neutral Pt

neutral ligand for the platinum (II) center, has been provided in

molecular structure of the cationic platinum (II) aquo system

tems

338

ketone derivatives.

24 h. Once the reaction temperature was decreased from 25 to 0

5 mol % of system

rapidly investigated. It has been known that the reaction using

ation of indole derivatives with nitroalkene derivatives, has been

been considered to be the suitable reaction temperature. Next, the

yields with good

the

Enantioselective AF-CA of indoles and α,β-unsaturated trifluoromethyl ketone derivatives.

Table 74

Enantioselective AF-CA of indoles and α,β-unsaturated trifluoromethyl ketone derivatives.

| Entry | R¹ | R² | Yield (%) | ee (%) |
|-------|----|----|-----------|--------|
| 1     | H  | H  | 95 (337a) | 84     |
| 2     | Me | H  | 98 (337b) | 16     |
| 3     | Bu | H  | 77 (337c) | 16     |
| 4     | H  | MeO| 36 (337d) | 77     |
| 5     | H  | Me | 99 (337e) | 85     |
| 6     | H  | F  | 91 (337f) | 72     |
| 7     | H  | Cl | 91 (337g) | 78     |
| 8     | H  | Br | 77 (337h) | 78     |
| 9     | H  | MeCO₂| 97 (337i)| 19     |
| 10    | H  | NC | 60 (337j)| 7      |

platinum (II) systems 338, that includes H₂O as an exchangeable neutral ligand for the platinum (II) center, has been provided in pure form from the reaction of the neutral Pt–I system with AgOTf in technical grade dichloromethane at ambient temperature. The molecular structure of the cationic platinum (II) aquo system 338 were identified via X-ray single-crystal analysis. The cationic systems 338 were used to the AF-CA of indole derivatives with nitroalkene derivatives. Among them, the aquo system 338 has been known to be efficient. With a catalyst loading of 5 mol%, various nitroalkylated indole derivatives have been generated in moderate yields with good ee (up to 83% enantioselectivity) [163]. In addition, there were no reports on the F-CA of indole derivatives with nitroalkene derivatives mediated by chiral Pt systems. Thus, the potential of the provided pure, chiral cationic pincer platinum (II) aquo system 338 in the current reaction has been examined. In the starting the reaction of indole to trans-β-nitrostyrene in toluene, that was the frequently applied solvent for metal-mediated alklylation of indole derivatives with nitroalkene derivatives, has been rapidly investigated. It has been known that the reaction using 5 mol % of system 338 as the catalyst afforded the product in an almost measurable yield with 69% enantioselectivity at 25 °C upon 24 h. Once the reaction temperature was decreased from 25 to 0 °C, a reduced yield of 84% has been provided with 5 mol % of system 338 upon 36 h, whereas the enantioselectivity was increased to 78% enantioselectivity. A more decline in temperature (0 °C to −10 °C) resulted in an extreme drop in the yield, but with a more improvement in enantioselectivity (81% vs 78%). Therefore, 0 °C has been considered to be the suitable reaction temperature. Next, the alklylation was extended to indole or indole derivatives with different aromatic nitroalkene derivatives. Generally, the reactions of indole (65–83% ee) with nitroalkene derivatives afforded ees higher than those of 5-bromo (57–73% ee) or 5-methoxyindole (34–64% ee) with the desired nitroalkene derivatives. Because of the substituent influence of the aromatic nitroalkene derivatives on the ees, it looked to be hard to establish a clear fashion. For

instance, in the case of indole or 5-methoxyindole, the nitroalkene that had a para-CH₃OC₆H₄ scaffold gave the highest ees compared with those including a Ph, p-F, p-Cl, or p-BrC₆H₄ scaffold based on same conditions, whereas in the case of 5-bromoindole, the nitroalkene bearing a p-FC₆H₄ scaffold afforded the highest enantioselectivity (Scheme 114, Table 75) [163].

2.14. Vanadium

Sasai and co-workers formerly described a chiral dinuclear vanadium systems for the catalyzed asymmetric oxidative homo-coupling reaction of 2-naphthols via a dual activation mechanism [164]. It was supposed that in the dinuclear V-mediated reaction, activation of 2-naphthol and imine by each V metal in the chiral template could lead to smooth hetero-coupling, affording a Betti adduct with excellent ee. The dinuclear V system (R,S,S)-240 was known to be a significant catalyst for the F–C-type reactions of imines and indole 5 [165].

Vanadium-mediated AF-C-type reactions have been developed by using the dinuclear V system (R,S,S)-240. The V system improved the F–C-type reaction of imine derivatives with 2-naphthol derivatives or indole derivatives to afford desired products with excellent ees. In 2013 Sasai and co-workers reported V

Table 75

AF-CA of indoles and nitroalkenes mediated by cationic pincer platinum (II) aquo complex 338.

| Entry | R¹, R² | Ar | Yield (%) | ee (%) |
|-------|--------|----|-----------|--------|
| 1     | H, H   | Ph | 99        | 69 (5) |
| 2     | H, H   | Ph | 84        | 78 (5) |
| 3     | H, H   | Ph | 43        | 81 (5) |
| 4     | H, H   | p-FC₆H₄| 73       | 65     |
| 5     | H, H   | p-ClC₆H₄| 86       | 67     |
| 6     | H, H   | p-BrC₆H₄| 60       | 71     |
| 7     | H, H   | p-MeOC₆H₄| 81       | 83     |
| 8     | H, H   | p-MeOC₆H₄| 93       | 65     |
| 9     | Br, H  | Ph | 89        | 58     |
| 10    | Br, H  | Ph | 77        | 70     |
| 11    | Br, H  | p-FC₆H₄| 70       | 73     |
| 12    | Br, H  | p-ClC₆H₄| 61       | 57     |
| 13    | Br, H  | p-BrC₆H₄| 69       | 62     |
| 14    | Br, H  | p-MeOC₆H₄| 61       | 57     |
| 15    | MeO, H | Ph | 72        | 34     |
| 16    | MeO, H | p-FC₆H₄| 58       | 36     |
| 17    | MeO, H | p-ClC₆H₄| 79       | 39     |
| 18    | MeO, H | p-BrC₆H₄| 70       | 46     |
| 19    | MeO, H | p-MeOC₆H₄| 65       | 64     |
| 20    | H, Me  | p-MeOC₆H₄| trace    | –      |
mediated AF-C-type reactions of N-tosyl imine derivatives and 2-naphthols or indoles. The dinuclear V system \((R_s S,S)_{240}\) acts as a chiral Lewis acid to improve F–C-type reactions with excellent ee (Scheme 115) [166].

With the optimum conditions in hand, \((R_s S,S)_{240}\) helped the F–C-type reaction with excellent ee of different functionalized aromatic N-tosylimine derivatives with 296a. 2-Thiophenyl N-tosylimine 122i, 6-bromo-2-naphthol 296b, and 7-methoxy-2-naphthol 296c were appropriate substrates. Besides, the dinuclear V system \((R_s S,S)_{240}\) was found to be a significant catalyst for the F–C-type reactions of imine derivatives and indole 4a. There are various methods of indole alkylation with tosylimine derivatives, but these methods from a high quantity of undesired bis-indole adduct [167]. It was known that alkylation by using catalyst 240 is much better since no such side-product has been identified. The highest enantioselectivity has been provided from the treatment of 4a and 2-bromophenyl N-tosylimine 122j, providing the desired product 242c with 91% enantioselectivity (Table 76).

The dinuclear V catalyst stimulated two various substrates in the F–C-type reaction to advance with excellent ee through a dual activation mechanism (Fig. 19) [166].

![Scheme 115. Vanadium-mediated AF-C-type reactions of imines and 2-naphthols or indoles.](image)

Table 76

| Entry | \(R^1\)   | Ar                  | Yield (%) | ee (%) |
|-------|-----------|---------------------|-----------|--------|
| 1     | H (296a)  | 4-ClC\(_6\)H\(_4\) (122a) | 70        | 241a   | 85     |
| 2     | H (296a)  | 4-BrC\(_6\)H\(_4\) (122b) | 70        | 241b   | 85     |
| 3     | H (296a)  | 4-FC\(_6\)H\(_4\) (122c) | 70        | 241c   | 76     |
| 4     | H (296a)  | 4-EIC\(_6\)H\(_4\) (122d) | 67  | 241d   | 81     |
| 5     | H (296a)  | 4-MeOC\(_6\)H\(_4\) (122e) | 70       | 241e   | 71     |
| 6     | H (296a)  | 3-CIC\(_6\)H\(_4\) (122f) | 70       | 241f   | 89     |
| 7     | H (296a)  | 2-CIC\(_6\)H\(_4\) (122g) | 70       | 241g   | 90     |
| 8     | H (296a)  | Ph (122h)           | 70       | 241h   | 71     |
| 9     | H (296a)  | 2-thiophenyl (122i) | 80       | 241i   | 60     |
| 10    | 6-Br (296b) | 4-ClC\(_6\)H\(_4\) (122a) | 77       | 241j   | 88     |
| 11    | 7-MeO (296b) | 4-ClC\(_6\)H\(_4\) (122a) | 8193     | 241k   | 61     |
| 12    | H (296a)  | 4-ClC\(_6\)H\(_4\) (122a) | 80       | 241a   | 76     |
| 13    | H (296a)  | 4-BrC\(_6\)H\(_4\) (122b) | 80       | 241b   | 76     |
| 14    | H (296a)  | 2-BrC\(_6\)H\(_4\) (122c) | 77       | 241c   | 91     |
| 15    | H (296a)  | 2-naphthyl (122k)  | 90       | 241d   | 64     |

![Scheme 116. Catalytic AF-CA of indole 4 and (E)-1-aryl-4-benzyloxybut-2-en-1-ones 244a-h catalyzed by \(\text{[(R)-245-Hf(OtBu)\(_4\)]}\).](image)

2.15. Hafnium

An extremely AF-CA of (E)-1-aryl-4-benzyloxybut-2-en-1-one derivatives and unprotected indole derivatives mediated by an efficient chiral \([\text{Hf}((R)-3,3’-Br_2 \text{BIN} \text{(OtBu)}\(_2\))]\) system was established to functionalize the C-3 position of the indole core with a side chain containing a 1,4-difunctionalized scaffold and a benzyl stereogenic center. The reaction was accomplished in moderate to high yields and high ees [168]. The expediency of this method has been exhibited with the formation of a tryptophol derivative. Relied on the optimization results, numerous (E)-1-aryl-4-benzyloxybut-2-en-1-one derivatives 244a-h and indole 4a have been selected, affording the corresponding alkylated indole derivatives in excellent ees. Remarkably, the electronic effect and the position of the group on the aromatic ring of the enone had slight effect on the enantioselectivity or yield of this reaction. Although, (E)-4-benzyloxy-1-(p-methoxyphenyl)but-2-en-1-one 244e treated slower, affording the corresponding product 246ae with merely 45% yield. Furthermore, the heteroaromatic compounds 244g and 244h provided the desired alkylated indole derivatives with excellent yields and ees (Scheme 116, Table 77) [168].

2.16. Magnesium

Special binary chiral phosphoric acid 248/magnesium fluoride [169] catalyst which assists efficacious catalysis of AF-C reactions of phenol derivatives 15 with >99% enantioselectivity and 82% yield (Scheme 117) [170]. A considerable synergistic influence was detected in the mixtures of two kinds of acids, in which an extremely active binary-acid catalyst was produced from two
separately inert acids. The generality of an enantioselective binary-acid-mediated AF-CA reaction has been examined with 248/magnesium fluoride in CH₂Cl₂ at −70 °C. Various β,γ-unsaturated-α-ketoester derivatives 13 were used in the treatments of free phenols 247a and 247b to afford the corresponding F-CA compounds 249a-j in moderate yields and excellent enantioselectivity. Remarkably, no reaction has been detected while 1,3-dimethoxybenzene has been applied (Table 78)[170]. Moreover, not only free phenols but also the enantioselective binary acid complex catalyst such as 248/magnesium fluoride might be effectively used in analogous F-C reactions with indole derivatives. Particularly, 0.5 mol % of magnesium fluoride serves for significant catalysis in several number of other reaction of indoles and β,γ-unsaturated-α-ketoester derivatives 13, giving the corresponding 1,4-addition products in 82−94% enantioselectivity and moderate yields (Scheme 118, Table 79)[170]. An AF-CA of indole derivatives and donor-acceptor cyclopropanes was demonstrated [171]. The reaction was mediated by pybox•MgI₂ [172]. Based on the optimization results, numerous indole derivatives having electronically different groups gave the corresponding enantioenriched alkylation compounds. Yields were

Table 77
Catalytic AF-CA of indole 4 and (E)-1-aryl-4-benzyloxybut-2-en-1-ones 144a-h catalyzed by [(R)-245-Hf(O(OTf)₄).]

| Entry | R¹ | Yield (%) | ee (%) |
|-------|----|-----------|--------|
| 1     | Ph | 90 (246aa) | 94     |
| 2     | 4-MeC₆H₄ | 86 (246ab) | 92     |
| 3     | 3-MeC₆H₄ | 98 (246ac) | 97     |
| 4     | 2-MeC₆H₄ | 81 (246ad) | 84     |
| 5     | 4-MeOC₆H₄ | 45 (246ae) | 87     |
| 6     | 4-BrC₆H₄ | 78 (246af) | 86     |
| 7     | 2-thienyl | 90 (246ag) | 92     |
| 8     | 2-furyl  | 93 (246ah) | 84     |

Table 78
F-CA reactions of various indoles 4 and β,γ-unsaturated α-ketoesters 105.

| Entry | R | R¹ | Yield (%) | ee (%) |
|-------|---|----|-----------|--------|
| 1     | H | Ph | 82 (250k) | 90 (R) |
| 2     | H | 2-FC₆H₄ | 87 (250l) | 94     |
| 3     | H | 4-ClC₆H₄ | 82 (250m) | 83     |
| 4     | H | 3,4-Cl₂C₆H₃ | 80 (250n) | 88     |
| 5     | H | 4-MeC₆H₄ | 78 (250o) | 87     |
| 6     | H | 4-PhC₆H₄ | 81 (250p) | 82     |
| 7     | 5-O-Me | Ph | 90 (250q) | 92     |
| 8     | 5-O-Me | Ph | 81 (250r) | 84     |
| 9     | 6-Cl | Ph | 83 (250s) | 92     |
| 10    | 6-Cl | 3,4-Cl₂C₆H₄ | 64 (250t) | 91     |

Scheme 117. F-CA reactions of 247a,b and β,γ-unsaturated α-ketoesters 13.

Table 79
F-CA reactions of various indoles 4 and β,γ-unsaturated α-ketoesters 105.

| Entry | R | R¹ | Yield (%) | ee (%) |
|-------|---|----|-----------|--------|
| 1     | H | Ph | 82 (250k) | 90 (R) |
| 2     | H | 2-FC₆H₄ | 87 (250l) | 94     |
| 3     | H | 4-ClC₆H₄ | 82 (250m) | 83     |
| 4     | H | 3,4-Cl₂C₆H₃ | 80 (250n) | 88     |
| 5     | H | 4-MeC₆H₄ | 78 (250o) | 87     |
| 6     | H | 4-PhC₆H₄ | 81 (250p) | 82     |
| 7     | 5-OMe | Ph | 90 (250q) | 92     |
| 8     | 5-OMe | Ph | 81 (250r) | 84     |
| 9     | 6-Cl | Ph | 83 (250s) | 92     |
| 10    | 6-Cl | 3,4-Cl₂C₆H₄ | 64 (250t) | 91     |

Scheme 118. F-CA reactions of various indoles 4 and β,γ-unsaturated α-ketoesters 105.

Scheme 119. An AF-CA of indole derivatives and donor-acceptor cyclopropanes.
usually excellent with the exception of electron-deficient indole derivatives containing halo or ester groups. In these cases, the decreased rates of alkylation are due to unproductive decomposition of 251a. More sterically challenging of 2- and 7-methylindole derivatives were well endured. In the previous situation a marginal decline in enantioselectivity happened, probably because of the high indole nucleophilicity. As detected by Kerr [173] and Ila [174], the existence of a 3-methyl group prompted cyclization of the putative intermediate providing pentannulation product 253s in a valuable er, however in modest yield and with poor de (Scheme 119) [171].

2.17. Rhodium

The half-sandwich aqua system (S_Rh,R_C)-[(η⁵-C₅Me₅)Rh((R)-Prophos)(H₂O)][SbF₆]₂ (Prophos = propane-1,2-diyldi(diphenylphosphane)) 255 mediated the enantioselective reaction of N-methyl-2-methylindole and trans-β-nitrostyrenes. Different trans-β-nitrostyrenes has been successively examined in the reaction with N-methyl-2-methylindole with by the Rh system 255. In the cases of 3- and 4-functionalized aromatic nitroalkene derivatives, excellent transformations have been provided. Possibly, because of steric hindrance, 2-substitution remarkably decreased both the yield and enantioselectivity. Enantioselection reduced for nitroalkene derivatives containing groups on the 3- and 4-positions but to a good extent for electron-donating groups and evidently as well as for electron-withdrawing groups (Scheme 120, Table 80) [175].

Table 80

| Entry | R       | Conversion (%) | ee (%) |
|-------|---------|----------------|--------|
| 1     | H       | 99 (93)        | 94     |
| 2     | 2-MeO   | 41 (37)        | 84     |
| 3     | 3-MeO   | >99 (94)       | 92     |
| 4     | 4-MeO   | >99 (93)       | 74     |
| 5     | 2-BnO   | 32 (25)        | 9      |
| 6     | 3-BnO   | >99 (91)       | 79     |
| 7     | 4-BnO   | 99 (94)        | 81     |
| 8     | 4-Me    | 99 (94)        | 71     |
| 9     | 4-OH    | 94 (90)        | 65     |
| 10    | 2-Cl    | 50 (46)        | 27     |
| 11    | 4-Cl    | 99 (91)        | 53     |
| 12    | 2-Br    | 54 (51)        | 38     |
| 13    | 4-Br    | >99 (90)       | 66     |
| 14    | 2,3-(MeO)₂ | 29 (25) | 74     |

Based on the experimental data, the catalytic cycle presented in Scheme 121 can be suggested. The linked H₂O molecule in 255 was shown using trans-β-nitrostyrene, providing the nitroalkene system 257. Indole attack on the stimulated C₈ of the coordinated nitroalkene, that renders aci-nitro system 258, is the enantioselectivity-limiting stage. Transformation of 258 with trans-β-nitrostyrene removes the aci-nitro ligand 259 and recreates system 257, which reinitiates the cycle. Lastly, free aci-nitro 259 impulsively rearrays to the F-C adduct 260 [175].

Scheme 120. AF-C reaction of N-Methyl-2-methylindole with trans-β-Nitrostyrenes.

Scheme 121. Proposed catalytic cycle for the AF-CA using 255.
2.18. Gold

Enders and co-workers in 2011 established a new approach to provide asymmetric tetracyclic indoles by developing organo- and Au-based catalysis via two sequential F–C type reactions [176]. It should be mentioned that this one-pot strategy permits insertion of a chiral center into a highly conjugated, tetracyclic system, without damaging the chiral integrity of the dibenzylic position. Furthermore, an uncommon 7-endo-dig cyclization reaction gave profound visions into Au catalysis on indole derivatives. Under the optimal reaction conditions, the generality of this unique, catalytic, enantioselective synthesis of pharmaceutically fascinating tetracyclic indoles were examined (Table 81). Generally, this one-pot, sequential, catalytic reaction were used for a wide range of substrates, having variable functionalities on the indole and the alkyne nitrostyrene component 261. 5-Methyl indole was provided in this tandem reaction, outstandingly (Table 81, 263b, 263f and 263j) with very high yields (over 90%). Other indole derivatives including 7-methylindole, 5-methoxyindole, and unfunctionalized indole derivatives, also afforded the corresponding satisfactory to high yields [176].

To confirm the industrial effectiveness of this unique, multienzymatic method, a 4 g scale reaction was performed to producing convincing evidence of its scalability. This system was achieved efficiently on a multigram scale at considerably lower catalyst loading (3 mol % of 262 and 5 mol % of [Au-(PPh3)]NTf2) with still high ee (93% ee) and yield (93%) comparable to those of the small-scale reaction (Table 81, 263b) [176].

| Entry | R1 | R2 | R3 | Yield (%) | ee (%) |
|-------|----|----|----|-----------|-------|
| 1     | 5-MeO | Ph  | H  | 78 (263a) | 97    |
| 2     | 5-Me  | Ph  | H  | 92 (263b) | 97    |
| 3     | H     | Ph  | H  | 51 (263c) | 97    |
| 4     | 7-Me  | Ph  | H  | 70 (263d) | 98    |
| 5     | 5-MeO | Ph  | F  | 67 (263e) | 97    |
| 6     | 5-Me  | Ph  | F  | 96 (263f) | 95    |
| 7     | H     | Ph  | F  | 81 (263g) | 98    |
| 8     | 7-Me  | Ph  | F  | 78 (263h) | 99    |
| 9     | 5-MeO | 3-tolyl | H | 80 (263i) | 97    |
| 10    | 5-Me  | 3-tolyl | H | 94 (263j) | 98    |
| 11    | H     | 3-tolyl | H | 79 (263k) | 97    |
| 12    | 7-Me  | 3-tolyl | H | 60 (263l) | 98    |

To confirm the industrial effectiveness of this unique, multienzymatic method, a 4 g scale reaction was performed to producing convincing evidence of its scalability. This system was achieved efficiently on a multigram scale at considerably lower catalyst loading (3 mol % of 262 and 5 mol % of [Au-(PPh3)]NTf2) with still high ee (93% ee) and yield (93%) comparable to those of the small-scale reaction (Table 81, 263b) [176].

Relied on the experiential data, as well as formerly reported investigations [177], a mechanism is suggested to clarify this multienzymatic system (Scheme 123). Initiating from C3,C2-unsubstituted indole derivatives and ortho-alkyne-functionalized nitrostyrenes, 261 acts as a bifunctional organocatalyst, analogous to a thiourea catalyst, providing a tight transition state TS 264 that is stabilised by multiple hydrogen-bonding interactions with the nitroolefin and the N–H of the attacking indole nucleophile. This locks the reacting partners in favoring an indole Si-attack and clarifies the excellent ee and (R)-configuration in the first F–C type reaction. Afterwards, the C3-substituted intermediate 265 is activated by the ρ-acidic [Au(PPh3)]NTf2, because of the presence of the auraphilic alkyne. The alkyne activation permits the C3 of indole to undergo a second F–C type reaction in a 6-endo-dig
fashion, providing a spirocyclic intermediate 267 [177b-h].

A group of axially chiral NHC–Au(I) systems was used to the enantioselective F–C/cyclization reaction of nitrogen-tethered 1,6-enyne derivatives 269 with indoles 4, 1,2-dichloroethane under mild conditions providing the relevant F–C and intramolecular cyclization products 271 in satisfactory yields and with good enantioselectivity under mild conditions [178]. Based on the optimal conditions, the scope of this Au(I) system-mediated enantioselective F–C/cyclization reaction was tested using a number of 1,6-enyne derivatives 269 and indoles 4. Once the R1 sulfonyl substituent was 4-bromobenzenesulfonyl (Bs), 4-nitrobenzenesulfonyl (Ns) or 2,4,6-tri-isopropylbenzenesulfonyl, the reaction was performed efficiently to give the relevant products 271b-d in satisfactory yields however accompanied by 2–44% enantioselectivity, demonstrating that the electronic properties and steric influences of the sulfonyl substituent exhibit an important role in this reaction. Furthermore, once R2 was either an electron-poor or -rich aromatic group, the reaction was achieved significantly to afford the relevant products 271e-i in satisfactory yields accompanied by 42–62% enantioselectivity and excellent dr, demonstrating that the electronic properties of the R2 substituent did not contain an important influence on the reaction result. Besides, the R3 substituent on the indole derivative could be an H atom, Bn substituent or Boc-masking substituent, affording the relevant products 271j-n in satisfactory yields along with 54–66% enantioselectivity and excellent dr. Merely once R2 was a hydrogen atom or an aliphatic substituent such as substrates 269j (R2 = H), 269k (2*R2 = Me), or 269l (2*R2 = Me), did the reaction give complex product mixtures (Scheme 124, Table 82) [178].

2.19. Miscellaneous

Catalytic AF-CA of pyrroles and nitroalkene derivatives have been explored by employing an efficient heterotrimetallic Pd–S–m–Pd catalyst using a simple chiral ligand 261 [179], to afford the corresponding products with up to 93% enantioselectivity and excellent yields [180]. Various functionalized nitroalkene derivatives 89b-e, including both electron-withdrawing and electron-donating substituents have been examined, and high yields and excellent ees have been detected for the corresponding products with 7a. Heteroaryl-functionalized nitroalkene derivatives 89f and 89g have been well endured for this reaction, and the thiophene-derived compound afforded the uppermost enantioselectivity. On the other hand, the alkyl-functionalized nitroalkene 89h afforded much poorer yield and selectivity. Moreover, functionalized pyrrole derivatives have been examined. The pyrrole containing an ethyl group at the 2-position was found appropriate for the F–C reactions, while in several reactions merely lower ees were obtained. However, the detected catalyst complex is appropriate for numerous substrates for both functionalized pyrroles and nitroalkene derivatives (Scheme 125, Table 83) [181].

In 2012, Rueping et al. reported the initial enantioselective Cα-mediated addition of indoles to trifluoroacrylate derivatives. The relevant products were provided in excellent yields and with satisfactory to high ees [182]. Based on the optimized reaction conditions, the generality of the enantioselective Ca3[PO4]2-mediated F-CA reaction was examined (Table 84). The current reaction was performed using 1-naphthyl-substituted[H3]-binol

![Scheme 124. The scope of the axially chiral Au system mediated enantioselective F–C/ cyclization reaction of 1,6-enynes 269 and indoles 4.](image-url)

| Entry | R1   | R2         | R2/R4 | Yield (%) | dr  | ee (%) |
|-------|------|------------|-------|-----------|-----|--------|
| 1     | Bs   | Ph (269b)  | 1-Me, H (4a) | 40 (271b) | 66:1 | (+)6   |
| 2     | Ns   | Ph (269c)  | 1-Me, H (4a) | 80 (271c) | 57:1 | (+)44  |
| 3     | Ph   | Ph (269d)  | 1-Me, H (4a) | 67 (271d) | 99:1 | (+)12  |
| 4     | Ts   | 1-Naph (269e) | 1-Me, H (4a) | 87 (271e) | (+)62 |
| 5     | Ts   | Mes (269f) | 1-Me, H (4a) | 90 (271f) | 99:1 | (+)62  |
| 6     | Ts   | 4-ClC6H4 (269g) | 1-Me, H (4a) | 83 (271g) | 99:1 | (+)62  |
| 7     | Ts   | 4-MeC6H4 (269h) | 1-Me, H (4a) | 87 (271h) | 99:1 | (+)60  |
| 8     | Ts   | 4-MeOC6H4 (269i) | 1-Me, H (4a) | 86 (271i) | 99:1 | (+)42  |
| 9     | Ts   | Ph (269a)  | H, 2-Me (4b) | 88 (271j) | 99:1 | (+)65  |
| 10    | Ts   | Ph (269a)  | H, 2-Me (4c) | 73 (271k) | 99:1 | (+)56  |
| 11    | Ts   | Ph (269a)  | H, 5-Br (4d) | 86 (271l) | 99:1 | (+)66  |
| 12    | Ts   | Ph (269a)  | H, 4-Et (4e) | 81 (271m) | 99:1 | (+)63  |
| 13    | Ts   | Ph (269a)  | 1-Boc, H (4f) | 72 (271n) | 99:1 | (+)54  |
| 14    | Ts   | H (269j)   | 1-Me, H (4a) | Complex | – | –     |
| 15    | Ts   | (269k)     | 1-Me, H (4a) | Complex | – | –     |
| 16    | Ts   | (269l)     | 1-Me, H (4a) | Complex | – | –     |
calcium phosphate Ca[276] as catalyst. Commonly, this reaction was performed well using different indoles containing electron-donating or electron-withdrawing substituents to give the corresponding products in high yields and with ee up to 89%. This approach permits access to biologically relevant fluorocontaining products that are interesting from both medicinal and agrochemical points of view. This new developed transition-metal-free approach addresses this challenge and gives a useful and mild approach for the formation of ester derivatives containing an α-trifluoromethyl as well as α-hydroxy scaffold, a substitution pattern that mimics a carboxylic acid (Scheme 126) [182].

3. Conclusion

The F-CA reaction is one of the oldest organic transformations discovered by French Charles Friedel and American chemists James Crafts in 1877. However its asymmetric variant only appeared in chemical literature in the middle 80s. Asymmetric F-CA is one of the most powerful methods of providing the special kinds of carbon-carbon bonds with sterecontrol. The capability to control the absolute configuration of the new stereogenic center in AF-CA is of foremost importance in the field of total synthesis of natural products. Besides, fruitful and exciting organocatalytic ideas for AF-CA reaction based on versatile organocatalysis for the achievement of high to excellent stereoselectivity are in much demand. The AF-CA increased by using the organometals is nowadays being employed as a common and efficient strategy for the synthesis of both optically active small compounds and extremely functionalized molecules. Two different strategies are taken to consideration catalyzed- AF-CA reaction: biocatalysis and organocatalysis. In this review we have focused on the field of metal-catalyzed AF-CA which has attracted much attention of organic synthetic chemists over the last few years due to both the novelty and selectivity of different metal catalyzed reactions. The recent impairing attempts toward metal-catalyzed AF-CA were collected, herein.

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