Organometal-catalyzed asymmetric Friedel-Crafts reactions

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ABSTRACT

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 renown 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-, diastereo- 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 unpredicted 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 in academia and industry. To the purpose, a plethora of organic reaction has been developed and much attention has been attracted. Much courtesy has been paid to those reactions which are constructing important organic scaffolds via C–C and C–N bonds with full stereocontrol and induction of excellent or even high chirality during bond formations [5]. Although the F-CA [6] is indeed one of the oldest (discovered in 1877) and well-established organic reaction and still used as one of the most imposing and fundamental reactions for especial carbon-carbon
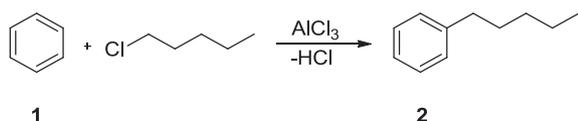
bond formation [7] its first catalyzed-stereoselective variants reported only during the past four decades [8] and incessantly being applied and seemed in chemical journals [8]. To be more precise the initial report of asymmetric catalyzed F–C alkylation appeared in the middle of 1980s [9]. To date, many laboratories in academia as well as industry have paid especial attention to develop new strategies to asymmetric catalyzed-F-CA by designing efficient and adaptable catalysts [8]. Notably, the asymmetric catalyzed-F-CA was performed via metal-catalyzed addition of an aromatic substrate to an electron deficient σ-(epoxide ring) and π-systems (1,2-carbonyl and 1,4-conjugate additions) in middle 80s. Since then, a massive advancement has been accomplished in the area of organocatalysis [10]. Nowadays, F-CA has opened a gate way to the discovery and development of novel, efficient and versatile asymmetric approaches for organization of such invaluable and pertinent transformations [11]. A remarkable and useful review in organocatalyzed asymmetric F–C was published 2001 [12]. It attracted much attention and stirred up the interest 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
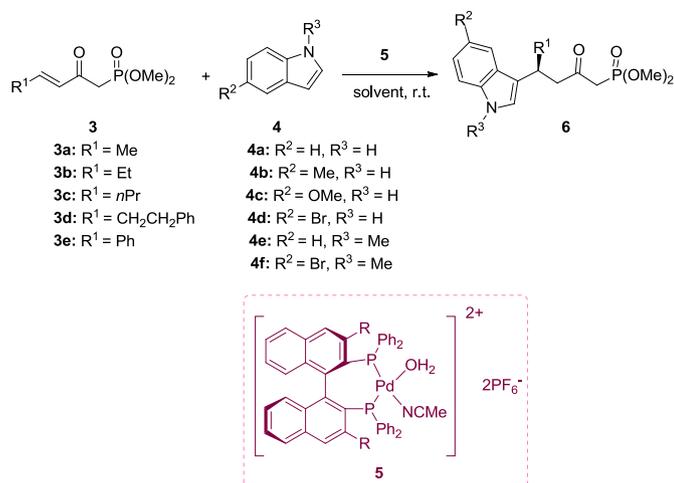
2.1. Palladium

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 α,β-unsaturated β-keto phosphonates **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 dicationic palladium complexes, containing sterically demanding diphosphine ligands as Lewis acid catalysts mediated the stereoselective F–C-type alkylation reaction of pyrroles and indoles with β,γ-unsaturated α-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 α-hydroxy esters through catalytic stereoselective ene sequences [16].

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

Scheme 1. AlCl₃-catalyzed reaction of amyl chloride and benzene developed by Friedel and Crafts.

Scheme 2. Catalytic AF-C reaction of indoles with β-keto phosphonates.

3a: R^1 = Me
3b: R^1 = Et
3c: R^1 = nPr
3d: R^1 = CH_2CH_2Ph
3e: R^1 = Ph

4a: R^2 = H, R^3 = H
4b: R^2 = Me, R^3 = H
4c: R^2 = OMe, R^3 = H
4d: R^2 = Br, R^3 = H
4e: R^2 = H, R^3 = Me
4f: R^2 = Br, R^3 = Me

Table 1
Catalytic AF-C reaction of indoles with β-keto phosphonates.

Entry	R^1	R^2, R^3	Solvent	Yield (%)	*ee* (%)
1	(**3a**) Me	H, H (**4a**)	THF	71 (**6a**)	99
2	(**3a**) Me	Me, H (**4b**)	Toluene	79 (**6d**)	99
3	(**3a**) Me	MeO, H (**4c**)	THF	92 (**6e**)	93
4	(**3a**) Me	Br, H (**4d**)	THF	75 (**6f**)	99
5	(**3a**) Me	H, Me (**4e**)	THF	71 (**6g**)	93
6	(**3a**) Me	Br, Me (**4f**)	THF	86 (**6h**)	93
7	Et (**3b**)	H, H (**4a**)	CH_2Cl_2	94 (**6i**)	85
8	Et (**3b**)	MeO, H (**4c**)	CH_2Cl_2	95 (**6j**)	93
9	Et (**3b**)	Br, H (**4d**)	Toluene	98 (**6k**)	93
10	Et (**3b**)	H, Me (**4e**)	CH_2Cl_2	95 (**6l**)	85
11	nPr (**3c**)	H, Me (**4e**)	THF	78 (**6m**)	90
12	CH_2CH_2Ph (**3d**)	H, H (**4a**)	THF	68 (**6n**)	99
13	Ph (**3e**)	H, H (**4a**)	THF	n.r.	–

3a

7a: R^4 = H
7b: R^4 = Me

8a: 72%, 99% *ee*
8b: 78%, 95% *ee*
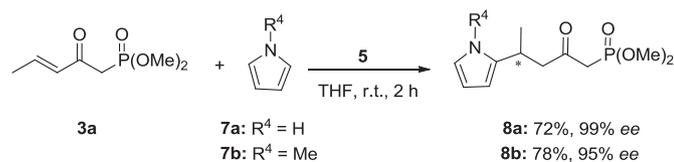
Scheme 3. AF-CA reaction of indole derivatives **7** using **5**.

ene reaction (Scheme 4) [17]. Using $Pd(PPh_3)_2(SbF_6)_2$ 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 pyrrole **7** and **13a** was performed in CH_2Cl_2, 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*

9a racemic

10

$Pd(PPh_3)_2(SbF_6)_2$
CH_2Cl_2, -78 °C, 4 h

Eq (1)

12a
99% yield
anti/syn 43/57

(*R*)-SEGPHOS-Pd: **11**

11
CH_2Cl_2, -78 °C, 24 h

Eq (2)

9a
>99% *ee*

10

12a
81% yield
anti/syn 92/8

ent-**11**
CH_2Cl_2, -78 °C, 24 h

Eq (3)

12a
94% yield
anti/syn 54/46

11
CH_2Cl_2, -40 °C, 9 h

Eq (4)

9b
98% *ee*

10

12b
92% yield
anti/syn 97/3

ent-**11**
CH_2Cl_2, -40 °C, 9 h

Eq (5)

12b
91% yield
anti/syn 40/60
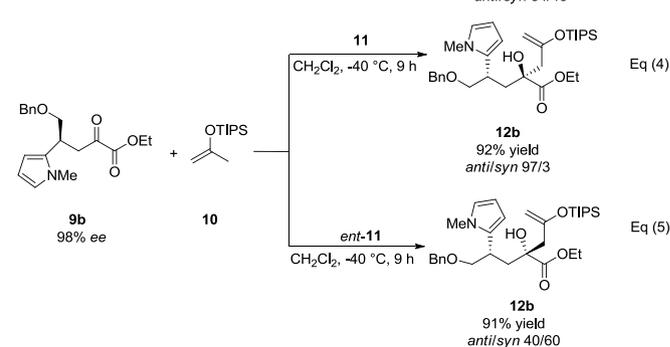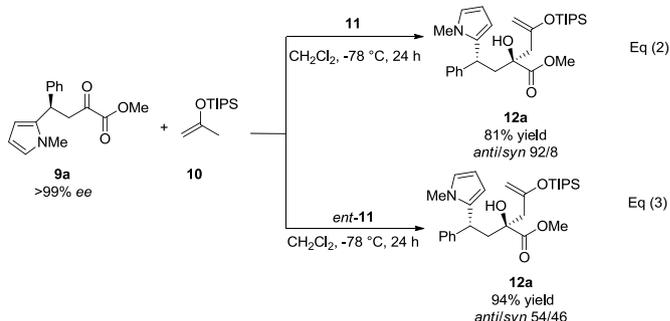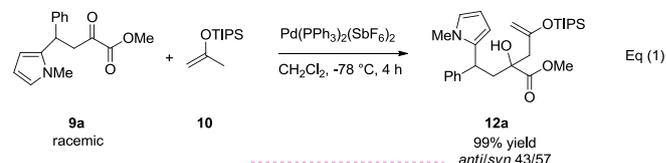
Scheme 4. Sequential catalytic carbonyl-ene reactions.

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 *ee*s. 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% *ee*s (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].
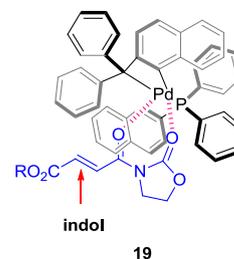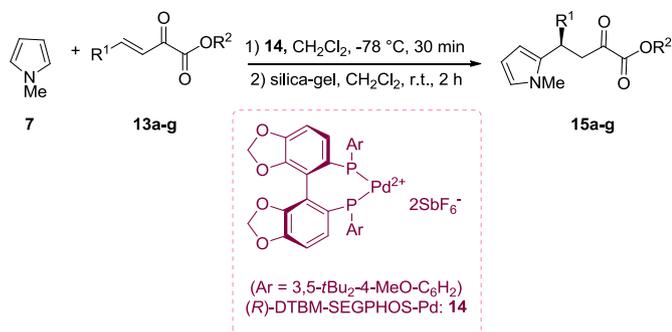
Scheme 5. Catalytic AF-CA of N-methyl pyrrole.

Table 2
Catalytic AF-CA of N-methyl pyrrole.

Entry	R^1	R^2	Yield (%)	ee (%)
1		Me (13a)	95	>99
2	(phenyl)	Me (13a)	94	98
3		Me (13a)	85	89
4		Et (13b)	90	98
5	(OBn)	Et (13b)	92	94
6		Me (13c)	83	98
	(Me-aryl)			
7	(NO$_2$-aryl)	Me (13d)	96	95
8	Me	Et (13e)	60	>99
9	Ph	Me (13f)	92	95
10	(phthalimide)	Me (13g)	97	84

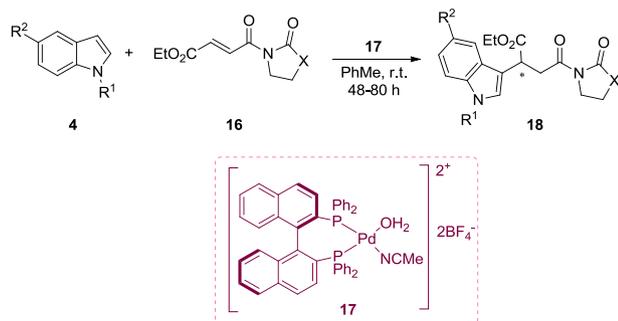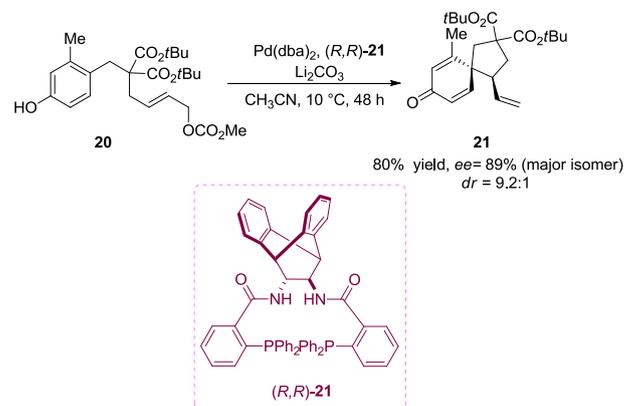Scheme 6. Catalytic AF-C reaction of indoles 4 and fumarate derivatives 16.

Table 3
Catalytic AF-C reaction of indoles 4 and fumarate derivatives 16.

Entry	R^1, R^2	X	Yield (%)	ee (%)
1	H, H (4a)	CH$_2$ (16a)	80 (18a)	83
2	H, H (4a)	O (16e)	87 (18e)	91
3	H, Me (4b)	O (16e)	88 (18f)	90
4	H, MeO (4c)	O (16e)	85 (18g)	91
5	H, Br (4d)	O (16e)	90 (18h)	83
6	Me, Br (4e)	O (16e)	81 (18i)	81

Fig. 1. Plausible transition-state model 19.

Scheme 7. An efficient catalytic stereoselective synthetic protocols for providing spirocyclohexadienones.

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% enantioselectivity (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
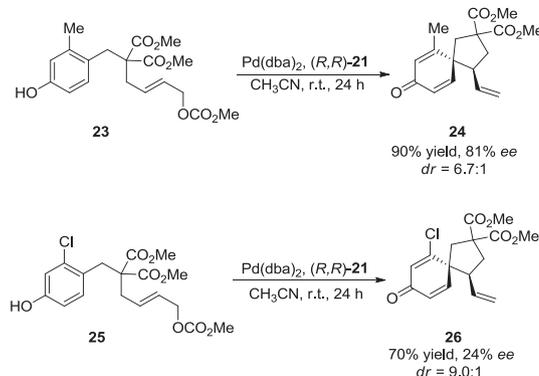
Scheme 8. Pd-catalyzed intramolecular ipso-F−C allylic alkylation of 23 or 25 using (R,R)-21.
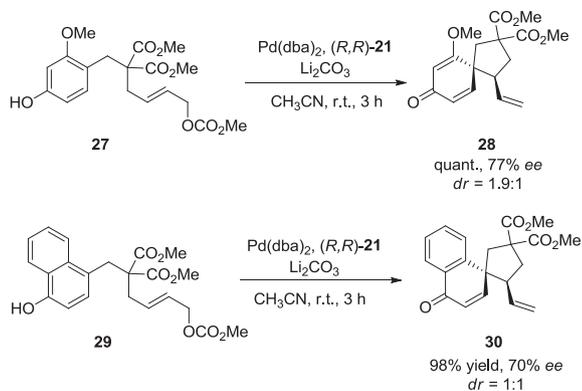
**Scheme 9.** Spirocyclization reactions of **27** and **29**.

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,
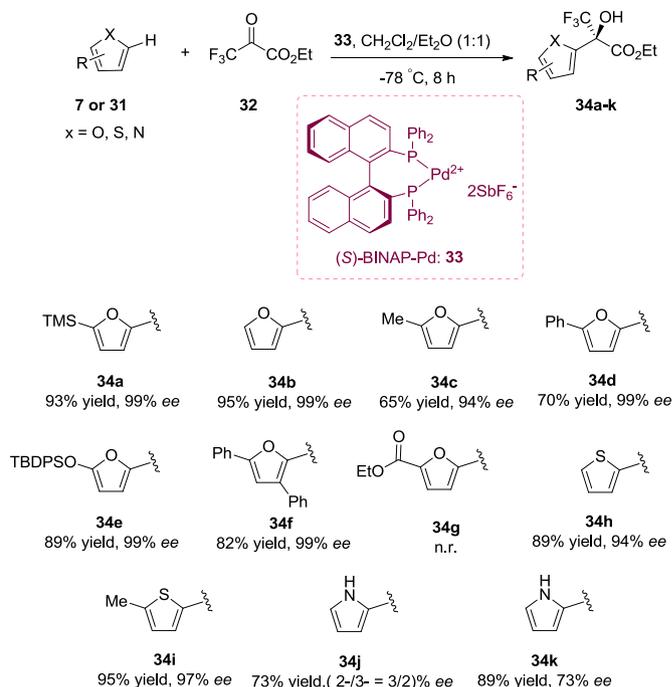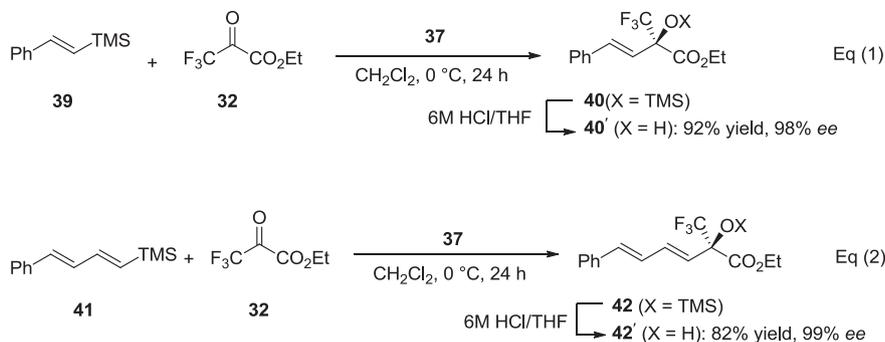

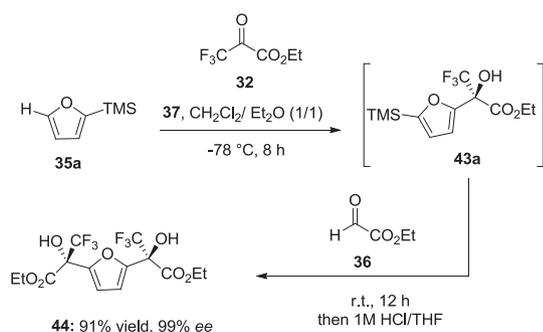**Scheme 10.** Scope of substrates in the catalytic AF-CA.
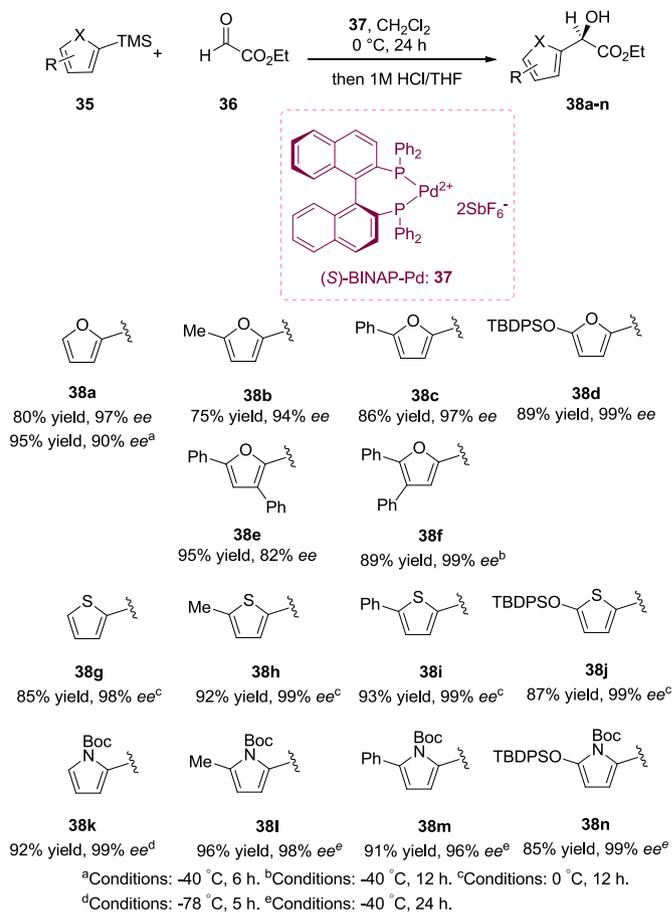
Scheme 11. Catalytic AF-C type reaction of 2-trimethylsilylated furan, thiophene, and pyrrole derivatives with ethyl glyoxylate.
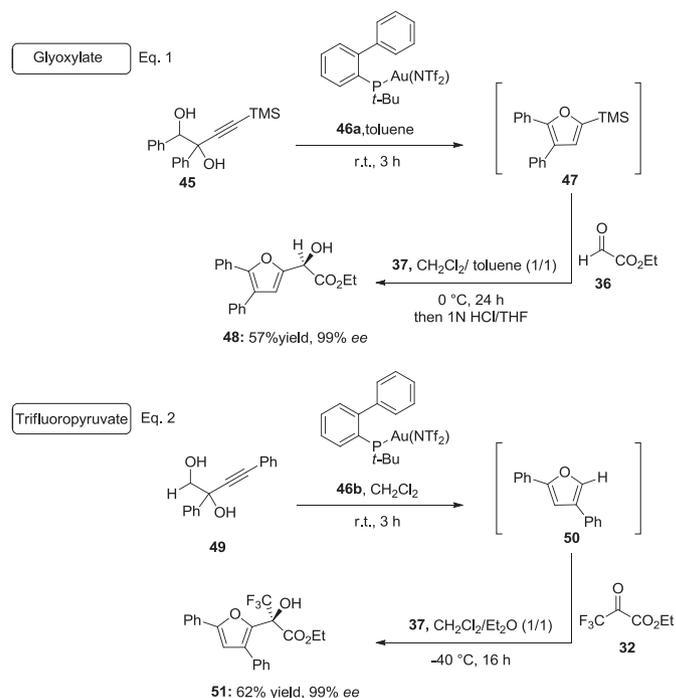
Scheme 12. Catalytic asymmetric alkenylation and dienylation.

Scheme 13. Two-directional reaction of furan **35a** with ethyl trifluoropyruvate followed by ethyl glyoxylate.

Scheme 14. Sequential catalytic intramolecular cyclization by a gold catalyst followed by F–C type reactions by a palladium catalyst.

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 CH$_2$Cl$_2$ and then was transferred to a solution of **45**, the F–C type reaction was proceeded to provide the hetero-arylated 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 (a*S*)-**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 (a*S*)-**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-NO$_2$-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].
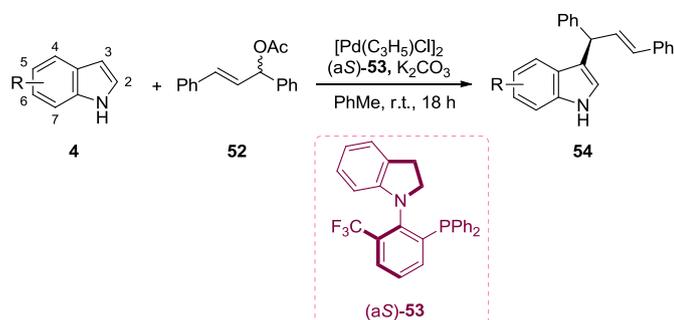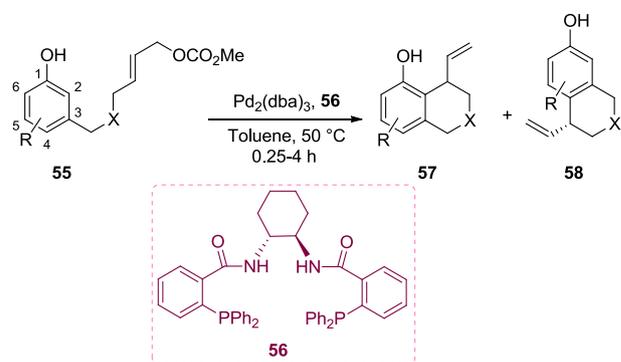
Scheme 15. Palladium-mediated asymmetric allylic alkylation of indoles and 1,3-diphenyl-2-propenyl acetate using (a*S*)-**53**.

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

Table 4
Palladium-mediated asymmetric allylic alkylation of indoles and 1,3-diphenyl-2-propenyl acetate using (a*S*)-**53**.

| 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 (**54j**)	86
13	5-Cl	73 (**54k**)	80
14	6-Cl	77 (**54l**)	86
15	6-F	83 (**54m**)	44
16	6-O$_2$N	n.r.	–
17	2-Ph	81 (**54n**)	86
18	2-Ph	88 (**54n**)	88

Table 5
Pd-mediated enantioselective intramolecular F–C type allylic alkylation reaction of phenols.

Entry	55, R	Yield (%)	57/58	*ee* (%)
1	H	73	**57a**	92
2	6-MeO	83	**57b**	85/15
3	4-Br, 6-MeO	80	**57c**	90
4	4-Br	61	**57d**	91
5	6-O$_2$N	30	**57e**	92
6	5-HO	93	**57f**	66
7	5-HO, 6-MeO	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		50	**57o**	38

Based on mild reaction conditions, Pd-mediated enantioselective intramolecular F–C type allylic alkylation of phenols has been achieved. By using Pd$_2$(dba)$_3$ with (1*R*,2*R*)-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 enantioselectivity. Once an electron-donating group has been introduced on the aromatic ring, a single isomer of **57** has been provided solely with moderate to high yields and enantioselectivity. For the substrate containing 6-methoxy substituent, the alkylation product has been produced in 83% yield with 2.6/1 regioselectivity preferring the ortho alkylated product **57b**. Using a strong electron-withdrawing substituent such as 6-NO$_2$, 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
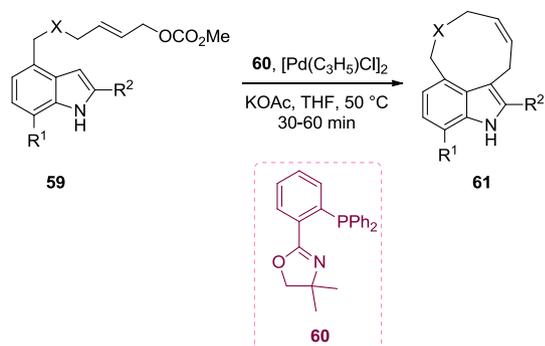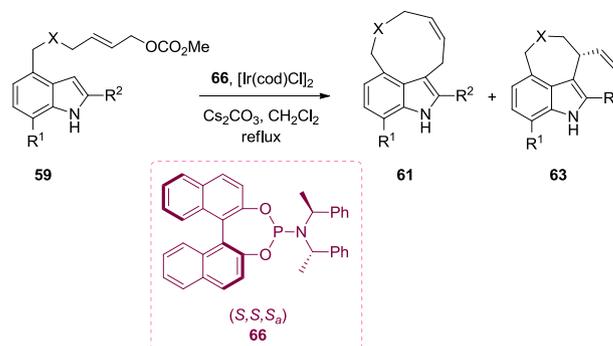
Scheme 17. Substrate scope for Pd-catalyzed F–C type allylic alkylation of indole fused.

Scheme 19. Substrate scope for Ir-catalyzed AF-C type allylic alkylation reaction of indole fused.

Table 6
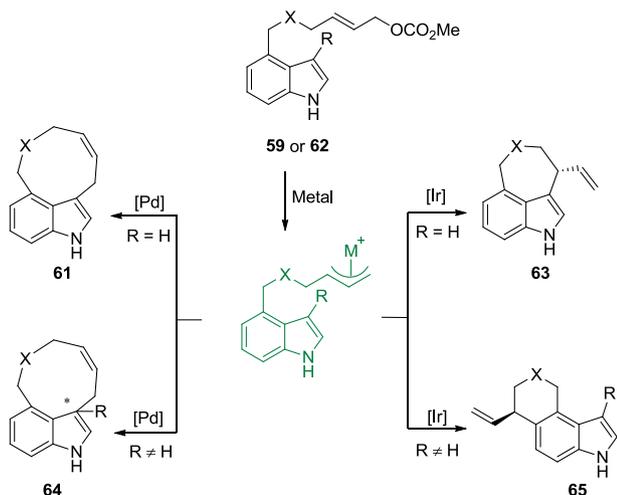Substrate scope for Pd-catalyzed F–C type allylic alkylation of indole fused.

Entry	X, R^1, R^2	Yield (%)
1	*n*Bn, H, H (**59a**)	70 (**61a**)
2	*N*-allyl, H, H (**59b**)	40 (**61b**)
3	*n*Bn, Me, H (**59c**)	68 (**61c**)
4	*n*Bn, F, H (**59d**)	57 (**61d**)
5	*n*Bn, Cl, H (**59e**)	60 (**61e**)
6	*n*Bn, H, Ph (**59f**)	64 (**61f**)
7	*n*Bn, H, 4-MeC$_6$H$_4$ (**59g**)	68 (**61g**)
8	*n*Bn, H, 4-ClC$_6$H$_4$ (**59h**)	68 (**61h**)
9	*n*Bn, H, Me (**59i**)	40 (**61i**)
10	*n*Bn, H, allyl (**59j**)	50 (**61j**)
11	C(CO$_2$Me)$_2$, H, H (**59k**)	70 (**61k**)

Table 7
Substrate scope for Ir-catalyzed AF-C type allylic alkylation reaction of indole fused.

Entry	X, R^1, R^2	63/66	Yield (%)	*ee* (%)
1	*N*Bn, H, H (**59a**)	2/98	60 (**63a**)	94
2	*N*-allyl, H, H (**59b**)	1/99	51 (**63b**)	94
3	*N*Bn, Me, H (**59c**)	1/99	46 (**63c**)	94
4	*N*Bn, F, H (**59d**)	4/96	64 (**63d**)	93
5	*N*Bn, Cl, H (**59e**)	6/94	62 (**63e**)	93
6	*N*Bn, H, Ph (**59f**)	2/98	78 (**63f**)	94
7	*N*Bn, H, 4-MeC$_6$H$_4$ (**59g**)	1/99	76 (**63g**)	91
8	*N*Bn, H, 4-ClC$_6$H$_4$ (**59h**)	2/98	68 (**63h**)	91
9	*N*Bn, H, Me (**59i**)	1/99	40 (**63i**)	95
10	*N*Bn, H, allyl (**59j**)	1/99	60 (**63j**)	97

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 corresponding products with moderate yields and excellent enantioselectivity. Various compounds containing both an aliphatic and aryl substituent at the 2-position of indole were applied in this reaction. Using 2-aryl indole, the corresponding products have been provided in moderate yields and excellent enantioselectivity. Also, 2-

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 **68** 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 allylic 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 a strong electron-withdrawing substituent (6-nitro) on the phenol moiety, the corresponding product has been produced with merely 25% yield, but high enantioselectivity (93%). Moreover, the carbon-tethered phenol **68l** gave the relevant product in 87% yield with 4.0/1 regioselectivity and 91% enantioselectivity (Scheme 21, Table 8) [34].
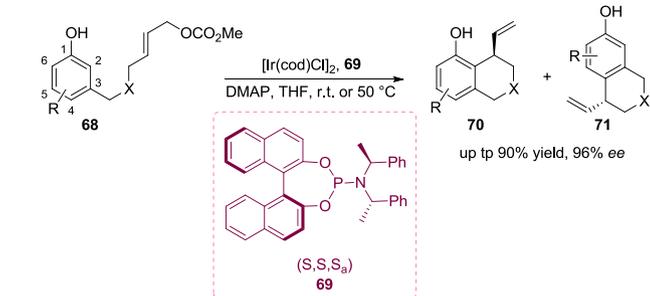
An extremely asymmetric synthesis of functionalized tetrahydrocarboline derivatives through iridium-mediated F–C type intramolecular enantioselective allylic alkylation reaction of 2-indolyl allyl carbonates was achieved. The reaction with ligand **73**

Scheme 18. Proposed diversity oriented formation of indole-based peri-annulated compounds.
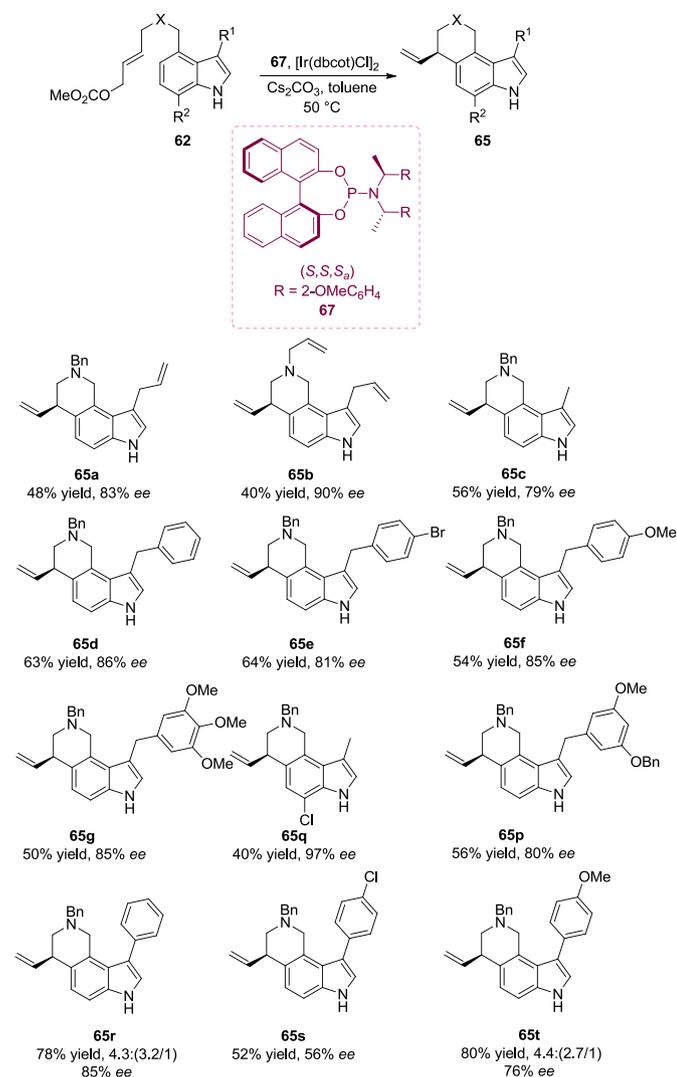
Scheme 20. Substrate scope for Ir-catalyzed F–C type allylic alkylation fused through C4–C5.

65a 48% yield, 83% ee

65b 40% yield, 90% ee

65c 56% yield, 79% ee

65d 63% yield, 86% ee

65e 64% yield, 81% ee

65f 54% yield, 85% ee

65g 50% yield, 85% ee

65q 40% yield, 97% ee

65p 56% yield, 80% ee

65r 78% yield, 4.3:(3.2/1) 85% ee

65s 52% yield, 56% ee

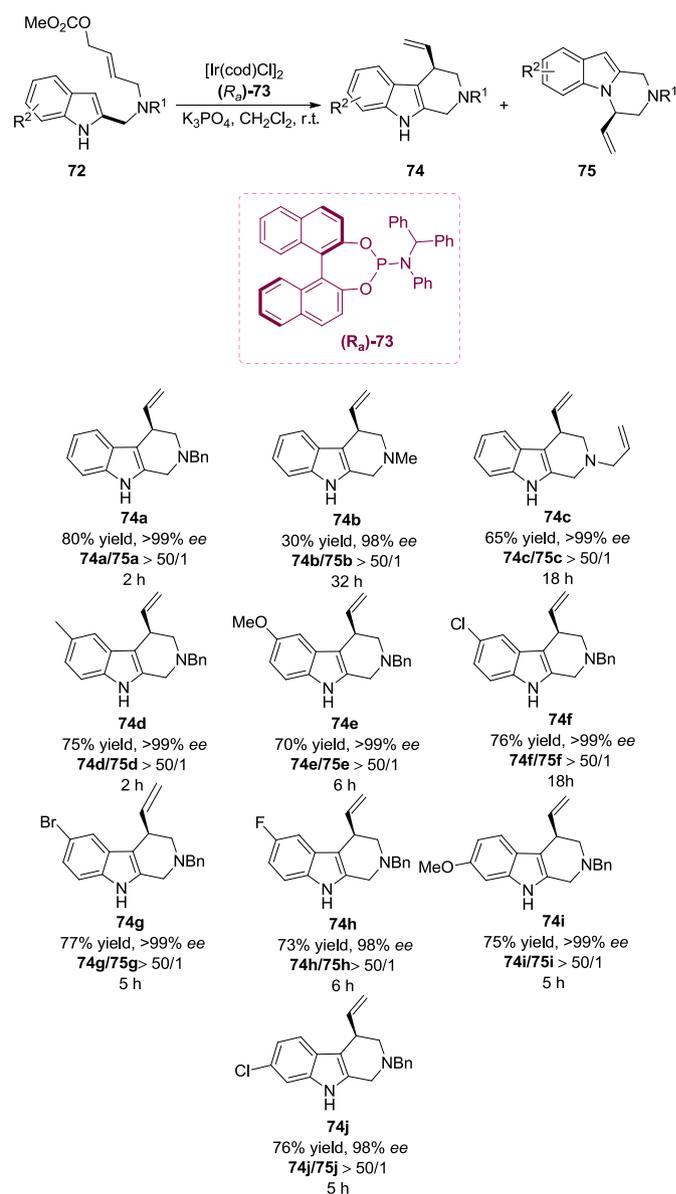**65t** 80% yield, 4.4:(2.7/1) 76% ee

Scheme 21. Intramolecular F–C-type allylic alkylation reaction of phenols.

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

Table 8
Intramolecular F–C-type allylic alkylation reaction of phenols.

Entry	X, R	70/71	Yield (%)	ee (%)
1	*N*Bn, H (**68a**)	4.8/1	84	92
2	*N*-allyl, H (**68b**)	6.0/1	88	92
3	*N*Bn, 2-MeO (**68c**)	3c	72	93
4	*N*Bn, 2-Cl (**68d**)	3d	80	94
5	*N*Bn, 6-MeO (**68e**)	4.0/1	82	95
6	*N*Bn, 6-O₂N (**68f**)	2f	25	93
7	*N*Bn, 4-Br (**68g**)	2g	78	89
8	*N*Bn, 2-Br,6-MeO (**68h**)	3h	50	96
9	*N*Bn, 4-Br,6-MeO (**68i**)	2i	80	92
10	*N*Bn, 5-HO (**68j**)	2j	90	86
11	*N*Bn, 5-HO, 6-MeO (**68k**)	2k	86	88
12	C(CO₂Me)₂, H (**68l**)	4.0/1	87	91

74a 80% yield, >99% ee **74a/75a** > 50/1 2 h

74b 30% yield, 98% ee **74b/75b** > 50/1 32 h

74c 65% yield, >99% ee **74c/75c** > 50/1 18 h

74d 75% yield, >99% ee **74d/75d** > 50/1 2 h

74e 70% yield, >99% ee **74e/75e** > 50/1 6 h

74f 76% yield, >99% ee **74f/75f** > 50/1 18h

74g 77% yield, >99% ee **74g/75g** > 50/1 5 h

74h 73% yield, 98% ee **74h/75h** > 50/1 6 h

74i 75% yield, >99% ee **74i/75i** > 50/1 5 h

74j 76% yield, 98% ee **74j/75j** > 50/1 5 h

Scheme 22. Asymmetric synthesis of functionalized tetrahydrocarboline derivatives through iridium -mediated F–C type intramolecular enantioselective.

provided the relevant products in moderate yields with high enantioselectivity (Scheme 22) [37].

Aqua-complexes (SM,RC)-[Cp*M((R)-prophos)(H₂O)][SbF₆]₂
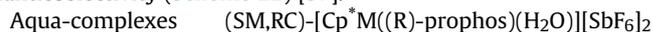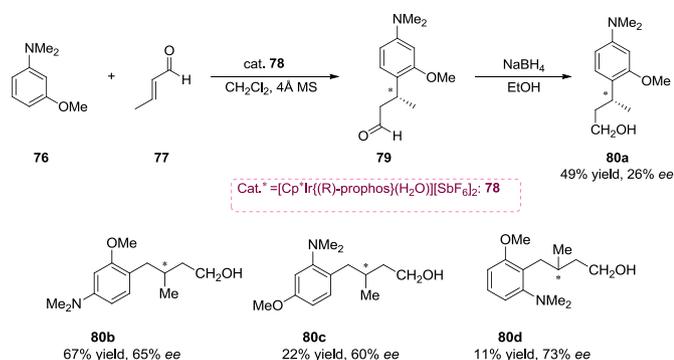
Scheme 23. Catalytic reaction of m-N,N-dimethylanisidine and trans-crotonaldehyde.

Scheme 24. Catalytic reaction of pyrroles and enals.

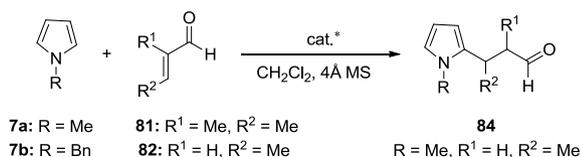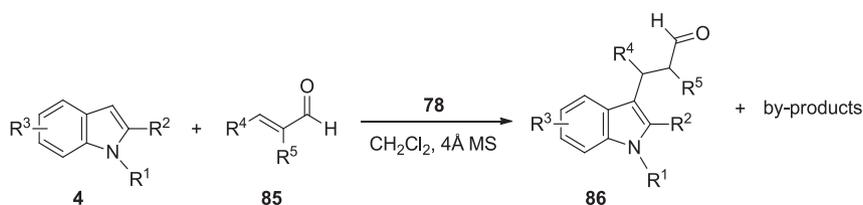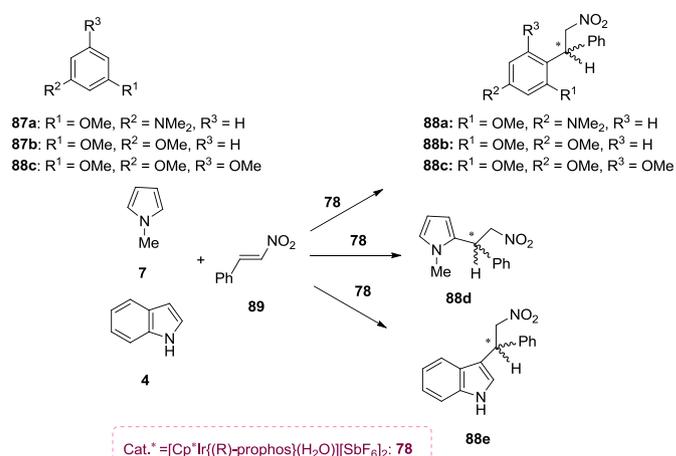(M = Rh, Ir) [38] mediated the alkylation of heteroaromatics and α,β-unsaturated aldehydes having aromatics nevertheless in some cases, combinations of adducts have been provided. Furthermore, complexes 83 and 78 have been applied to stimulate nitroalkenes for the AF-CA reaction of a variety of aromatics and hetero-aromatics, especially, 1,3,5-trimethoxybenzene. For this compound, the monoalkylated product has been produced in quantitative chemical yield with ees of up to 73% enantioselectivity being accomplished [39]. CH$_2$Cl$_2$ 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 mon-osubstituted 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% enantiose-lectivity 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 de-rivatives 87a-c, N-methyl pyrrole 7a and indole utilizing the Ir complex 78 as a catalyst precursor. CH$_2$Cl$_2$ was applied as solvent and reactions have been happen, under 4 Å MS. Only mono-substituted 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. Enan-tiomeric 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
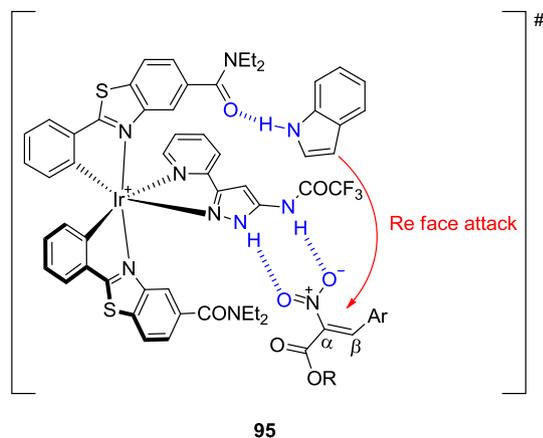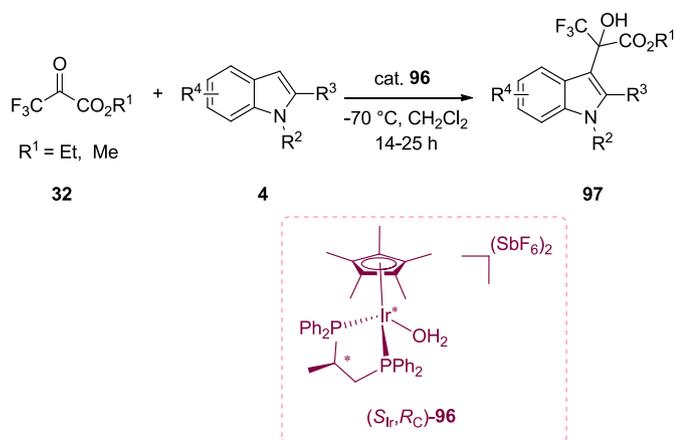

Scheme 26. Reaction of several aromatics and heteroaromatics with trans-β-nitrostyrene.

Scheme 25. Catalytic reaction of indoles and enals.

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

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)$_2$O (89m)	24	89 (91m)	70
10	2,4-(Me)$_2$O (89n)	22	22 (91n)	51
11	2,5-(Me)$_2$O (89o)	24	95 (91o)	40
12	3,4-(Me)$_2$O (89p)	22	92 (91p)	67
13	3,4-(Bn)$_2$O (89q)	25	96 (91q)	20
14	3,5-(Bn)$_2$O (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-Cl (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)$_2$ (89 ab)	49	2.5 (91 ab)	3
24	2-Cl,6-F (89ac)	118	50 (91ac)	47
25	2-F$_3$C (89ad)	96	22 (91ad)	9

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 [(η^5-C$_5$Me$_5$)Ir((R)-Prophos)(H$_2$O)][SbF$_6$]$_2$ **96** with up to 84% enantioselectivity [41]. Remarkably, experimental and theoretical data assisted to suggest a

Scheme 28. A stereoselective AF-CA transformation of 2-nitro-3-arylacrylates and indoles mediated by a metal-templated hydrogen bonding catalyst.

Fig. 2. Proposed transition state of the AF-CA catalyzed by ʌ-Ir.

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

Table 10
AF-C hydroxyalkylation reactions of indoles and pyruvates.

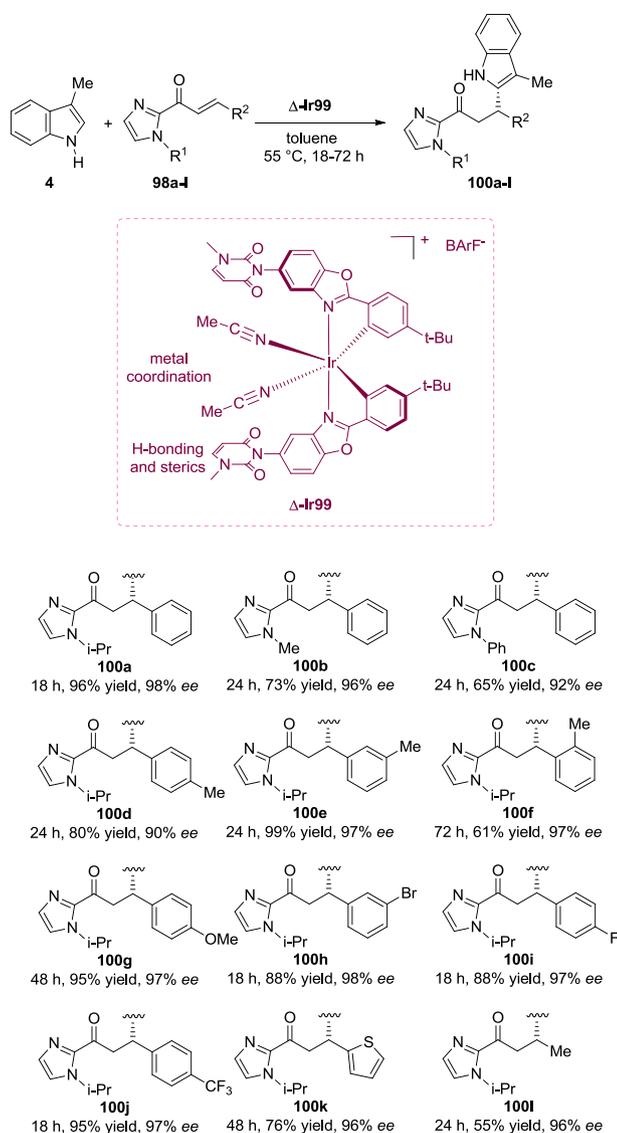| Entry	Cat.	R^1	R^2, R^3, R^4	Yield (%)	ee (%)
1	1	Et	H, H, H	>99 (**97a**)	65
2	1	Et	Me, H, H	>99 (**97b**)	47
3	1	Et	H, Me, H	>99 (**97c**)	76
4	1	Et	Me, Me, H	96 (**97d**)	52
5	1	Et	H, H, 5-MeO	>99 (**97e**)	71
6	1	Et	H, H, 5-Cl	96 (**97f**)	76
7	1	Et	H, Me, 5-MeO	97 (**97g**)	55
8	1	Et	H, Me, 5-Cl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

2 mol %. As an application, the straightforward synthesis of a chiral pyrrolo-[1,2-α]indole is shown in Scheme 30 [44]. Various α,β-unsaturated 2-acyl imidazole derivatives, by using 2 mol % of **Δ-Ir99** in toluene provide α,β-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 β-position in yields of 55–99% yield and 92–98% enantioselectivity [44].

A highly active catalyst for the AF-CA of indole derivatives and β,β-disubstituted nitroalkene derivatives was described. Bis-cyclometalated 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 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 C_2-symmetrical to increase the atom economy of this catalyst moiety (two catalytic centers per 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 Λ-(R,R)-**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 *ee*s. This is consistent with the suggested mechanism in which a hydrogen bond between the indole nitrogen-hydrogen and the carboxamide 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 β,γ-unsaturated α-ketoester derivatives has been achieved using a chiral Cu system [47], to give the alkylated derivatives of pyrrole with high *ee*s and moderate yields [48]. Based on the optimal reaction condition, the substrate generality of β,γ-unsaturated α-ketoester derivatives for the F-CA has been examined. First, the electronic influence has been tested

mechanism, comprising the Brønsted-acid activation of the pyruvate carbonyl using the protons of the linked H_2O molecule in **96**. In this reaction H_2O was not separated throughout the reaction and, thus, the catalytic reaction should happen without straight interaction of the metal and the substrates. Then, reactions of **32a** or its methyl analogue 3,3,3-trifluoropyruvate **32b** with different indole derivatives **4** have been achieved in a substoichiometric method. Normally, at −70 °C, with a catalytic loading of 5 mol%, reactions were completed in 15 min. Good enantioselectivity have been provided in all reactions. This catalyst can be applied for both electron-withdrawing and donating groups at the 5 position of the indole, without any decrease in enantioselectivity. But *N*-methylation decreased the chiral induction, but not as much as formerly reported [42], demonstrating that the NH functionality does not play any significant role in the hydroxyalkylation reaction. Remarkably, the homologous Ir system [43] (S_{Rh},R_C)-[(η⁵-C₅Me₅)Ir((R)-Prophos)(H_2O)][SbF₆]₂ was considered as an efficient catalyst for this approach that gave analogous selectivity (Scheme 29, Table 10) [41].

A chiral-at-metal bis-cyclometalated Ir system combines electrophile activation through metal coordination with nucleophile activation through hydrogen bond production. This bifunctional chiral Lewis acid/hydrogen bond-catalyzed permits the challenging asymmetric 2-alkylation of 3-functionalized indole derivatives with α,β-unsaturated 2-acyl imidazole derivatives in up to 99% yield and with up to 98% enantioselectivity at a catalyst loading of

Scheme 30. F–C reaction of indole Generality of this reaction using α,β-unsaturated 2-acyl imidazoles.

Scheme 31. Substrate scope with (Z)1-aryl-2-nitroacrylic esters and indoles using catalyst ʌ-(R,R)-Ir **101**.

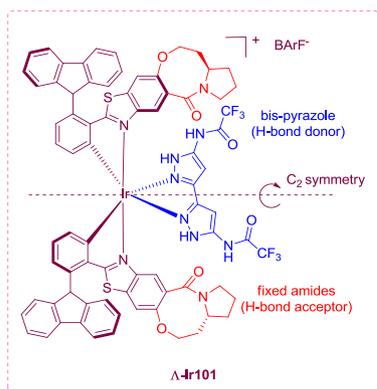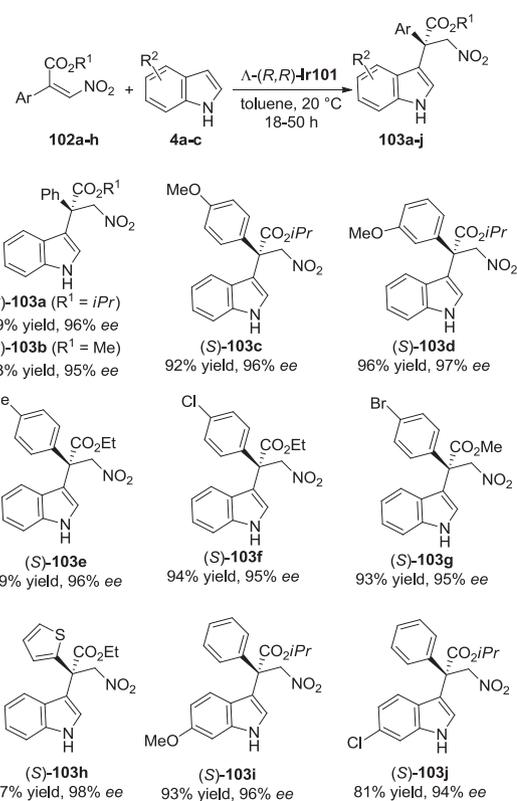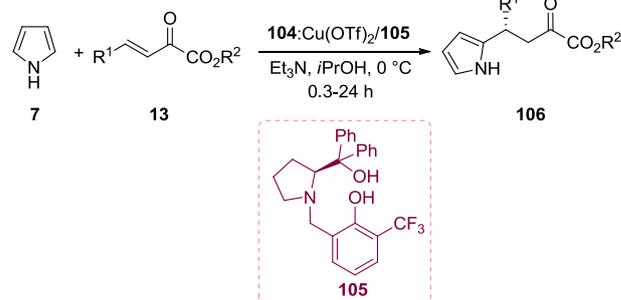**Scheme 32.** AF-CA of pyrrole and β,γ-unsaturated α-ketoester derivatives.

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

by changing the *para*-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 *ee*s 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. Next, various ester groups R^2 demonstrated slight effect on the alkylation in terms of the yields and *ee*s (Scheme 32, Table 11) [48].

The extremely AF-CA of pyrrole and isatins mediated by the tridentate Schiff base/copper catalyst has been achieved in 2014 [49]. Hexafluoroisopropanol (HFIP) has been applied as a crucial additive to increase the enantioselectivity. [50] *N*-Methylisatins having various groups at the 5-, 6-, or 7-positions treated with pyrrole and afforded the desired compounds in over 90% enantioselectivity with nearly measureable yields. In a former report, shifting the substituent group to the 4-position of *N*-methyl isatin

Table 11
AF-CA of pyrrole and β,γ-unsaturated α-ketoester derivatives.

Entry	R^1, R^2	Yield (%)	ee (%)
1	Ph, *i*Pr (**13a**)	89 (**106a**)	98
2	*p*-MeC$_6$H$_5$, *i*Pr (**13b**)	73 (**106b**)	96
3	*p*-MeOC$_6$H$_5$, *i*Pr (**13c**)	63 (**106c**)	94
4	*p*-FC$_6$H$_5$, *i*Pr (**13d**)	79 (**106d**)	97
5	*p*-ClC$_6$H$_5$, *i*Pr (**13e**)	84 (**106e**)	91
6	*p*-BrC$_6$H$_5$, *i*Pr (**13f**)	79 (**106f**)	94
7	*p*-O$_2$NC6H5, *i*Pr (**13g**)	96 (**106g**)	96
8	*p*-F$_3$CC$_6$H$_5$, *i*Pr (**13h**)	86 (**106h**)	94
9	*m*-ClC$_6$H$_5$, *i*Pr (**13i**)	82 (**106i**)	98
10	*o*-ClC$_6$H$_5$, Et (**13j**)	72 (**106j**)	89
11	*m*-BrC$_6$H$_5$, *i*Pr (**13k**)	84 (**106k**)	98
12	*o*-BrC$_6$H$_5$, Et (**13l**)	85 (**106l**)	96
13	2-naphthyl, *i*Pr (**13m**)	84 (**106m**)	96
14	2-thienyl, *i*Pr (**13n**)	66 (**106n**)	94
15	phenylpropyl, Et (**13o**)	66 (**106o**)	94
16	Ph, Me (**13p**)	87 (**106p**)	98
17	Ph, Et (**13q**)	80 (**106q**)	94
18	Ph, Bn (**13r**)	80 (**106r**)	95
19	Ph, *t*-Bu (**13s**)	70 (**106s**)	95

Table 12
The AF-CA of isatins and pyrrole using **108**.

Entry	R^1	R^2	Yield (%)	ee (%)
1	H	Me	96 (**109a**)	99
2	5-F	Me	97 (**109b**)	98
3	5-Cl	Me	99 (**109c**)	99
4	5-Br	Me	95 (**109d**)	98
5	5-I	Me	97 (**109e**)	91
6	5-O$_2$N	Me	98 (**109f**)	94
7	5-Me	Me	98 (**109g**)	99
8	6-Br	Me	97 (**109h**)	99
9	7-Br	Me	96 (**109i**)	99
10	7-F$_3$C	Me	96 (**109j**)	88
11	4,7-Cl$_2$	Me	94 (**109k**)	82
12	H	Bn	97 (**109l**)	95
13	H	H	99 (**109m**)	69
14	5-Me	H	91 (**109n**)	63
15	5-Br	H	95 (**109o**)	56
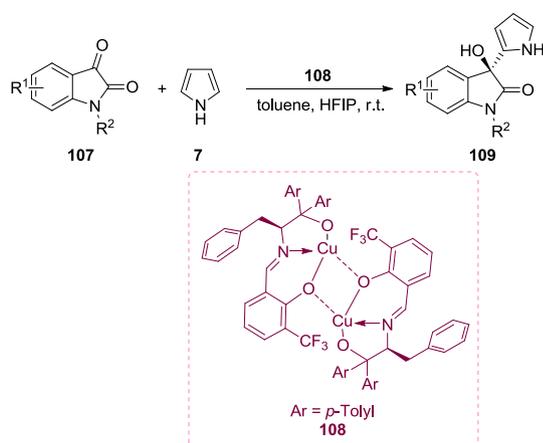
Scheme 33. The AF-CA of isatins and pyrrole using **108**.

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 Brønsted 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) **114** [55], and azabis(oxazoline) **115a** [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 1.05 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 suboptimal 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) (*S,S*)-**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 Cu$_2$Eu 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 **119aa** 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-naphthol 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
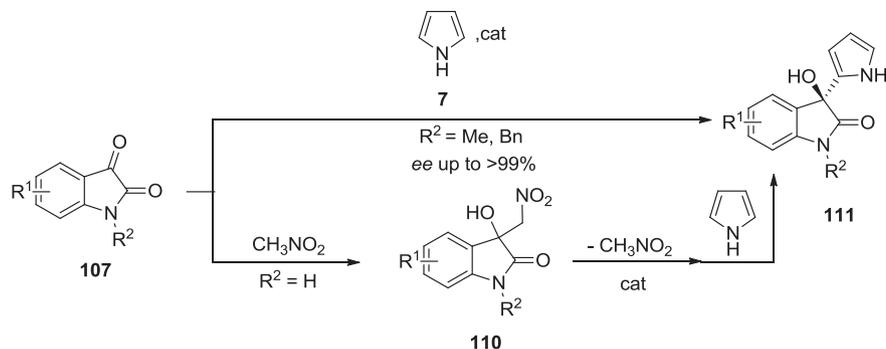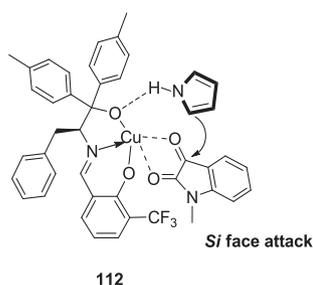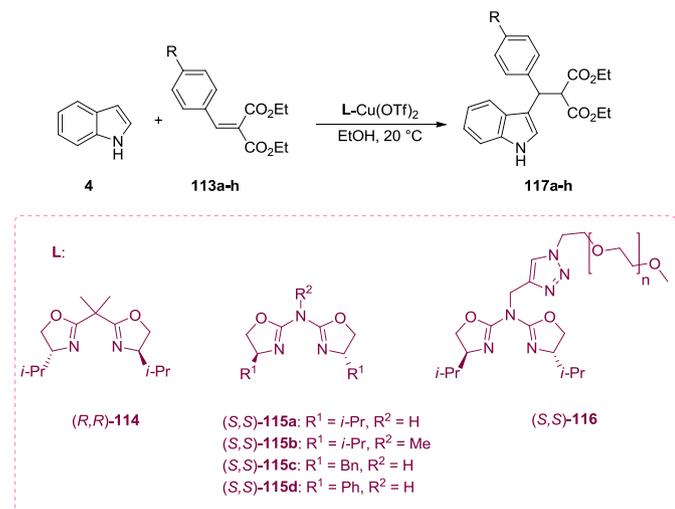
Scheme 34. A Probable mechanism for the FC-A reaction.

Fig. 4. A hypothetical action mode of the transition state of the AF-CA of N-methylatin with pyrrole.
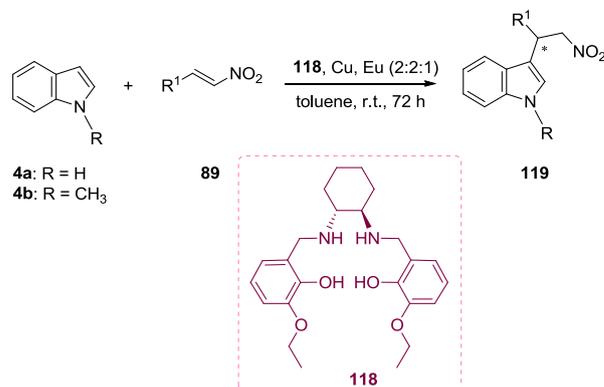
Table 13
AF-CA of indoles and benzylidene malonate derivatives.

Entry	Ligand	R	Yield (%)	ee (%)
1	(R,R)-**114**	H	89	99 (R)
2	(S,S)-**115a**	H	97	99 (S)
3	(R,R)-**114**	H	93	90 (R)
4	(S,S)-**115a**	H	90	98 (S)
5	(S,S)-**115b**	H	84	77 (S)
6	(S,S)-**115c**	H	90	81 (S)
7	(R,R)-**115d**	H	63	57 (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	(S,S)-**115a**	Me	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 35. AF-CA of indoles and benzylidene malonate derivatives.

Scheme 36. Catalytic AF-C reaction of various indoles and nitroalkenes.

Table 14
Catalytic AF-C reaction of various indoles and nitroalkenes.

Entry	R	R^1	Yield (%)	ee (%)
1	H	Ph (**89a**)	62 (**119aa**)	55
2	H	4-FC$_6$H$_5$ (**89b**)	52 (**119 ab**)	63
3	H	4-ClC$_6$H$_5$ (**89c**)	67 (**119ac**)	53
4	H	4-BrC$_6$H$_5$ (**89d**)	65 (**119ad**)	53
5	H	4-MeOC$_6$H$_5$ (**89e**)	53 (**119ae**)	49
6	H	2-furyl (**89f**)	72 (**119af**)	63
7	H	2-thiophenyl (**89g**)	87 (**119 ag**)	70
8	Me	Ph (**89a**)	86 (**119ba**)	53
9	Me	4-FC$_6$H$_5$ (**89b**)	88 (**119bb**)	71
10	Me	4-ClC$_6$H$_5$ (**89c**)	82 (**119bc**)	63
11	Me	4-BrC$_6$H$_5$ (**89d**)	76 (**119bd**)	64
12	Me	4-MeOC$_6$H$_5$ (**89e**)	68 (**119be**)	74
13	Me	2-furyl (**89f**)	72 (**119bf**)	79
14	Me	2-thiophenyl (**89g**)	63 (**119bg**)	80

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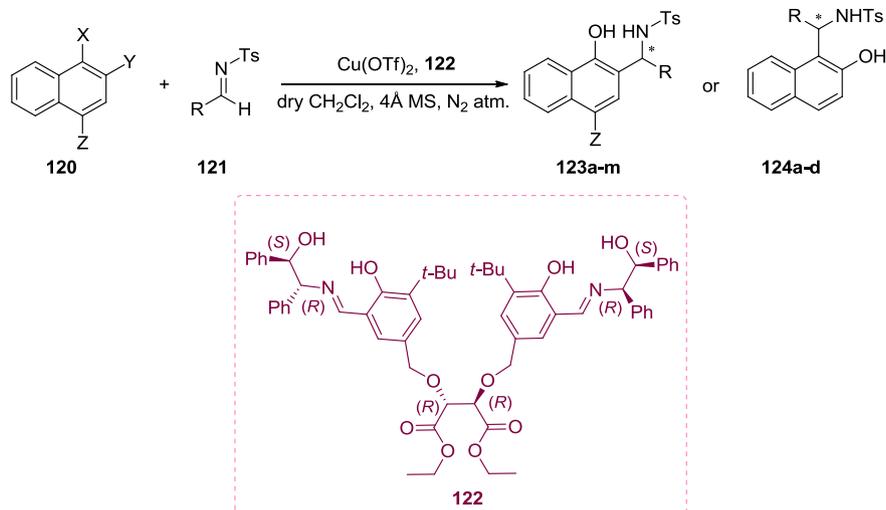
Scheme 37. Asymmetric addition of 1-naphthol or 2-naphthol with tosyl adimine with dinuclear Cu(II)-**122** catalyst.

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

Entry	X, Y, Z, R	Yield (%)	ee (%)
1	HO, H, H, 3-$O_2NC_6H_4$	98	99 (**123a**)
2	HO, H, H, 4- $O_2NC_6H_4$	95	96 (**123b**)
3	HO, H, H, 4-BrC_6H_4	84	96 (**123c**)
4	HO, H, H, 4-BrC_6H_4	95	90 (**123d**)
5	HO, H, H, 2-ClC_6H_4	80	88 (**123e**)
6	HO, H, H, 4-ClC_6H_4	90	96 (**123f**)
7	HO, H, H, Ph	82	92 (**123g**)
8	HO, H, H, 2-MeC_6H_4	79	85 (**123h**)
9	HO, H, H, 4-$MeOC_6H_4$	82	90 (**123i**)
10	HO, H, H, 4-MeC_6H_4	80	92 (**123j**)
11	HO, H, H, nC_3H_7	70	78 (**123k**)
12	HO, H, H, 3-$O_2NC_6H_4$	95	96 (**123l**)
13	HO, H, MeO, 3-$O_2NC_6H_4$	85	93 (**123m**)
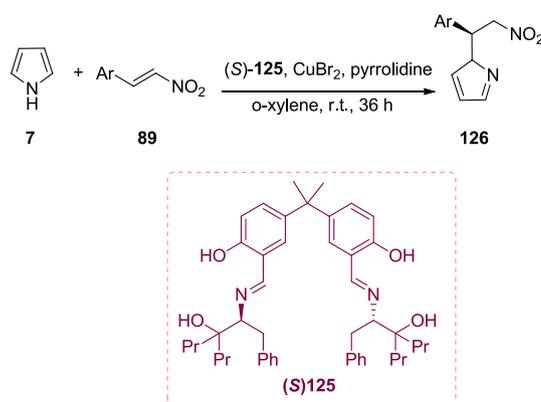
Scheme 38. Catalytic AF-CA of pyrrole **7** with various nitroalkenes.

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 **623** 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 $NaIO_4/RuCl_3$ 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 Cu^{2+} ion has been linked to the nitroalkene *via* the oxygen atom of the $-NO_2$ 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 $Ni(ClO_4)_2\cdot 6H_2O$/bipyridine system as an efficient catalyst provided allylic alcohols in high yields. The enantioselective reaction has been mediated by chiral copper(II)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 16
Catalytic AF-CA of pyrrole **7** with various nitroalkenes.

Entry	Ar	Conv (%)	MB (%)	Product	ee (%)
1	Ph	>99	94	**126a**	94 (>99)
2	2-BrPh	>99	94	**126b**	94
3	3-BrPh	>99	95	**126c**	91
4	4-BrPh	>99	95	**126d**	91
5	2-ClPh	>99	92	**126e**	85
6	3-ClPh	>99	89	**126f**	92
7	4-ClPh	>99	92	**126g**	95 (>99)
8	2-MePh	>99	89	**126h**	88
9	3-MePh	>99	94	**126i**	88
10	4-MePh	>99	90	**126k**	91
11	2-MeOPh	75	89	**126l**	79
12	3-MeOPh	>99	88	**126m**	90
13	4-MeOPh	77	90	**126n**	90
14	2-O2NPh	>99	90	**126o**	67
15	3-O2NPh	>99	89	**126p**	94
16	4-O2NPh	>99	92	**126r**	92 (>99)
17	1-naphthyl	>99	90	**126s**	88
18	2-naphthyl	>99	91	**126t**	90
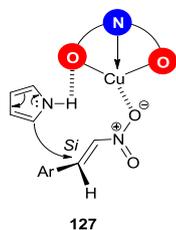
Fig. 5. Postulated transition state of the AF-CA catalyzed by (*S*)-2-Cu complex.

Scheme 39. Scope of the AF-CA.

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*s (64—75%). Although, the yields have been disapprovingly influenced by the electron-withdrawing groups, 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, 130 al, 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*-sulfonyl aziridine derivatives as alkylating agents was achieved by using the system of Cu-(CH3CN)4BF4/(*S*)-Segphos as a catalyst [64]. Various optically active tryptamines were provided in moderate to high yields and *ee*s 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 *ee*s. Various substituents on the benzene ring of *N*-tosylaziridine derivatives **131** were well-endured, while the *ee*s were affected disapprovingly by the electron-donating groups. The enantioselectivity levels for products **133e-h** bearing electron-donating substituents were marginally poorer than those of products **133b-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
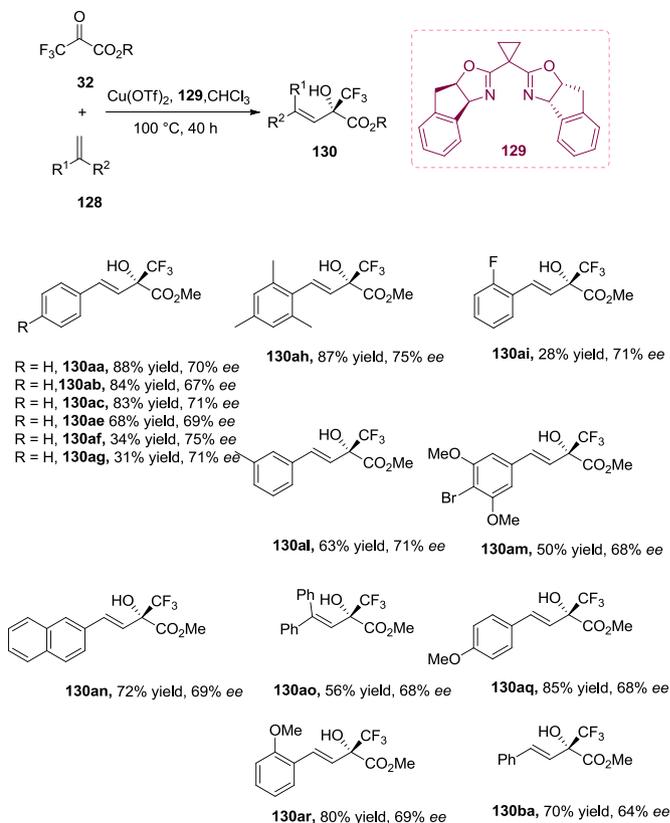
substituent resulted in desired product **133j** in 87% *ee*, demonstrating that enantioselectivity was influenced by steric hindrance (Scheme 40, Table 17) [64].

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 *ee*s 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 *ee*s based on catalysis of a novel tridentate Schiff base-Cu
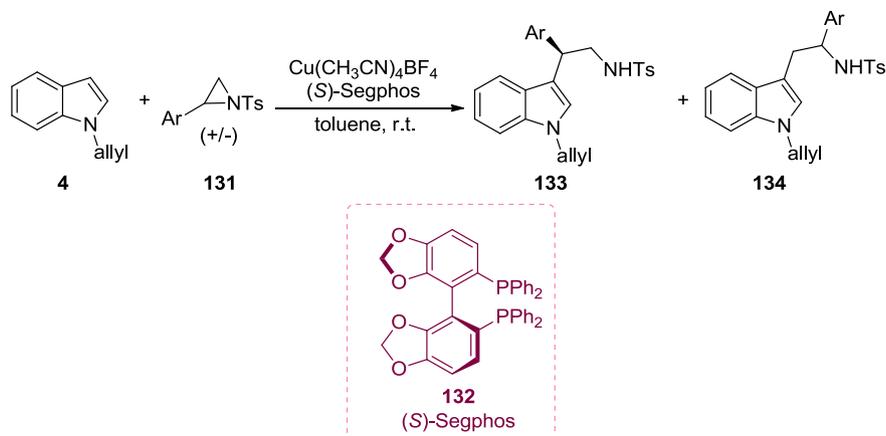
Scheme 40. AF-CA of indoles and *N*-sulfonylaziridine derivatives using the system of Cu-(CH₃CN)₄BF₄/(*S*)-Segphos as a catalyst.

Table 17
AF-CA of indoles and *N*-sulfonylaziridine derivatives using the system of Cu-(CH₃CN)₄BF₄/(*S*)-Segphos as a catalyst.

Entry	Ar	Yield (%)	*ee* (%)
1	Ph (**131a**)	**73** (**133a**)	94 (*R*)
2	4-BrC₆H₄ (**131b**)	65 (**133b**)	95
3	4-ClC₆H₄ (**131c**)	73 (**133c**)	95
4	4-FC₆H₄ (**131d**)	88 (**133d**)	91
5	4-*t*BuC₆H₄ (**131e**)	75 (**133e**)	90
6	4-AcO−C₆H₄ (**131f**)	75 (8:1) (**133f**)	88
7	3-MeC₆H₄ (**131g**)	72 (**133g**)	92
8	3-MeOC₆H₄ (**131h**)	65 (**133h**)	86
9	3-ClC₆H₄ (**131i**)	88 (**133i**)	93
10	2-MeC₆H₄ (**131j**)	77 (5:1) (**133j**)	87
11	2-naphthyl (**131k**)	74 (13:1) (**133k**)	80

Table 18
The **136**-Cu(OTf)₂ catalyzed AF-C reaction of indole derivatives and alkylidene malonates.

Entry	R¹	R²	R³	Yield (%)	*ee* (%)
1	H	4-MeOC₆H₄	H	99	98
2	H	4-MeC₆H₄	H	99	99
3	H	4-FC₆H₄	H	99	>99
4	H	3-BrC₆H₄	H	90	75
5	H	2-ClC₆H₄	H	65	71
6	5-MeO	Ph	H	99	73
7	5-Me	Ph	H	99	43
8	5-Cl	Ph	H	55	40
9	6-Cl	Ph	H	67	74
10	H	Ph	Me	75	45
11	H	Ph	Bn	60	33
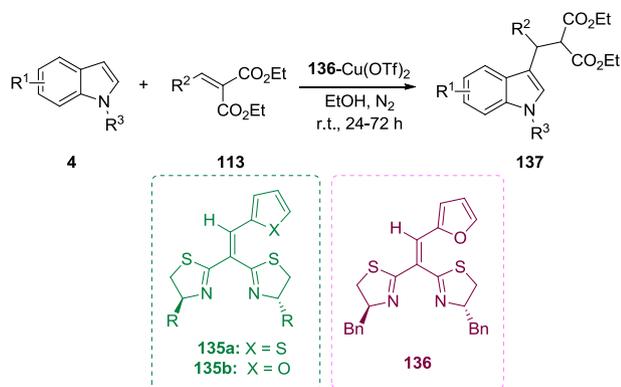
Scheme 41. The **136**-Cu(OTf)₂ catalyzed AF-C reaction of indole derivatives and alkylidene malonates.
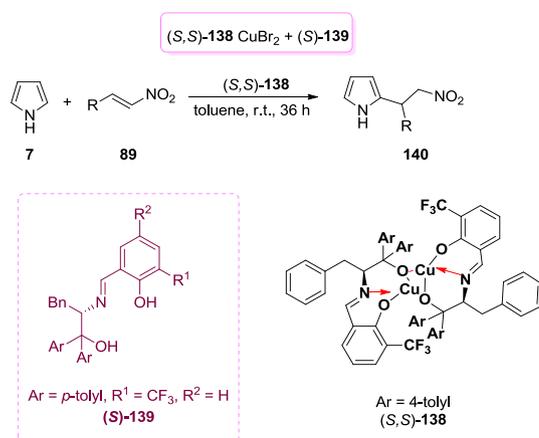
Scheme 42. The AF-CA of pyrrole and nitroalkenes.

system. 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 *ee*s 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)

Table 19
The AF-CA of pyrrole and nitroalkenes.

Entry	R	Yield (%)	ee (%)
1	2-BrC$_6$H$_4$ (**89a**)	86 (86) (**140aa**)	92 (92)
2	2-ClC$_6$H$_4$ (**89b**)	92 (92) (**140 ab**)	93 (92)
3	2-MeOC$_6$H$_4$ (**89c**)	70 (72) (**140ac**)	92 (90)
4	3-ClC$_6$H$_4$ (**89d**)	99 (99) (**140ad**)	96 (96)
5	3-MeOC$_6$H$_4$ (**89e**)	89 (88) (**140ae**)	94 (97)
6	3,4-Cl$_2$C$_6$H$_3$ (**89f**)	99 (99) (**140af**)	96 (96)
7	4-FC$_6$H$_4$ (**89g**)	93 (94) (**140 ag**)	94 (94)
8	4-ClC$_6$H$_4$ (**89h**)	96 (96) (**140ah**)	96 (95)
9	4-BrC$_6$H$_4$ (**89i**)	99 (99) (**140ai**)	97 (97)
10	4-F$_3$CC$_6$H$_4$ (**89j**)	99 (99) (**140aj**)	97 (98)
11	4-MeC$_6$H$_4$ (**89k**)	75 (78) (**140ak**)	94 (92)
12	4-MeOC$_6$H$_4$ (**89l**)	72 (73) (**140 al**)	94 (94)
13	Ph (**89m**)	92 (93) (**140am**)	94 (94) (*S*)
14	2-furyl (**89n**)	90 (**140an**)	92
15	2-thienyl (**89o**)	85 (88) (**140ao**)	91 (94)
16	1-naphtyl (**89p**)	75 (77) (**140ap**)	92 (91)
17	2-naphtyl (**89q**)	90 (90) (**140aq**)	91 (91)
18	*n*Pr (**89r**)	99 (99) (**140ar**)	96 (97)
19	*i*Pr (**89s**)	97 (98) (**140as**)	94 (94)
20	Me(CH$_2$)$_5$ (**89t**)	99 (99) (**140 at**)	95 (98)
21	PhCH$_2$CH$_2$ (**89u**)	99 (99) (**140au**)	95 (98)
22	Cyclohexyl (**89v**)	89 (**140av**)	90
23	TBDPSOCH$_2$ (**89w**)	97 (98) (**140aw**)	98 (98)
24	TBDPSOCH$_2$(CH$_2$)$_2$ (**89x**)	98 (98) (**140ax**)	98 (98)
25	Ph (**89m**)	92 (93) (**140ay**)	94 (94) (*R*)

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
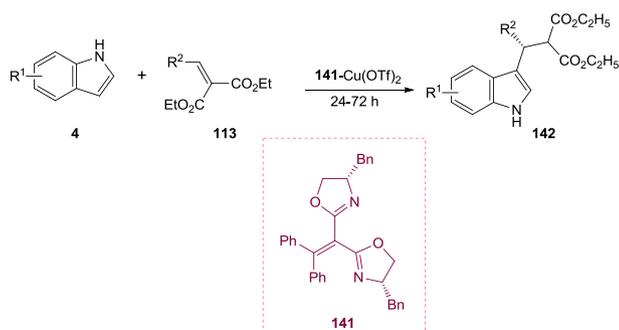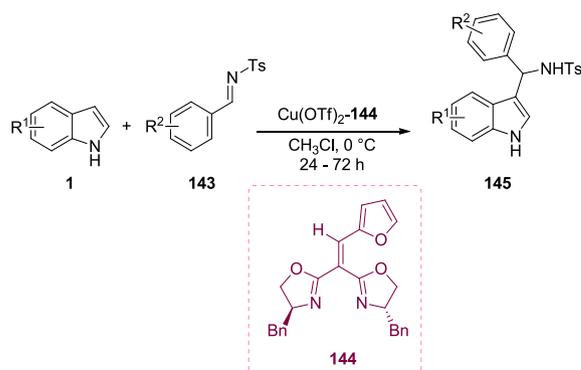
Table 20
Complex **141**-Cu(OTf)$_2$ catalyzed F−C reaction of indole derivatives and alkylidene malonates.

Entry	R^1	R^2	Yield (%)	ee (%)
1	H	*p*-MeC$_6$H$_4$	99	96
2	H	*p*-FC$_6$H$_4$	99	98
3	H	*p*-BrC$_6$H$_4$	90	98
4	H	*o*-ClC$_6$H$_4$	75	87
5	H	*o*-FC$_6$H$_4$	80	99
6	H	*o*-MeC$_6$H$_4$	90	79
7	H	*m*-FC$_6$H$_4$	99	78
8	H	*m*-MeC$_6$H$_4$	90	79
9	5-MeO	Ph	99	<99
10	5-Me	Ph	99	<99.9
11	7-Me	Ph	99	98
12	5-Cl	Ph	90	75
13	6-Cl	Ph	90	70
14	6-MeCO$_2$	Ph	90	82
15	5-MeO	*o*-MeC$_6$H$_4$	99	91

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)-L**144** and a benzyl substituent. Following this methodology a series of indoles and aldimines have been prepared as shown Scheme 44 [70]. Once R^2 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═N 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 **143i** 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-CF$_3$-benzylidene)-4-methylbenzene sulfonamide **143n-q** and 5-methoxyindole, 5-methylindole, 5-chloroindole, and 6-chloroindole afforded the corresponding products in high yields

Scheme 43. Complex **141**-Cu(OTf)$_2$ catalyzed F−C reaction of indole derivatives and alkylidene malonates.

Scheme 44. **144**-Cu(OTf)$_2$ mediated F−C reaction of indoles and *N*-sulfonyl aldimines.
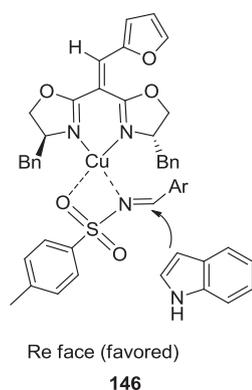
Table 21
144-Cu(OTf)$_2$ mediated F−C reaction of indoles and *N*-sulfonyl aldimines.

Entry	R^1	R^2	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$_3$C (**143f**)	85 (**145f**)	96
6	H	*m*-O$_2$N (**143g**)	81 (**145g**)	89
7	H	*m*-NC (**143h**)	90 (**145h**)	94
8	H	*m*-Br (**143i**)	85 (**145i**)	90
9	H	*m*-F$_3$C (**143j**)	84 (**145j**)	88
10	H	*o*-F$_3$C (**143k**)	80 (**145k**)	96
11	H	H (**143l**)	70 (**145l**)	90
12	H	*p*-MeO (**143m**)	0 (**145m**)	–
13	5-MeO	*p*-F$_3$C (**143n**)	85 (**145n**)	91
14	5-Me	*p*-F$_3$C (**143o**)	80 (**145o**)	95
15	5-Cl	*p*-F$_3$C (**143p**)	82 (**145p**)	97
16	6-Cl	*p*-F$_3$C (**143q**)	86 (**145q**)	>99

Table 22
The AF-CA of indoles and various nitroalkenes.

Entry	R^1	R^2	Yield (%)	*ee* (%)
1	H (**4a**)	Ph (**89a**)	99 (**148a**)	95 (*R*)
2	H (**4a**)	4-ClC$_6$H$_4$ (**89b**)	96 (**148b**)	92
3	H (**4a**)	3-ClC$_6$H$_4$ (**89c**)	94 (**148c**)	94
4	H (**4a**)	2-ClC$_6$H$_4$ (**89d**)	99 (**148d**)	97
5	H (**4a**)	4-MeC$_6$H$_4$ (**89e**)	99 (**148e**)	93
6	H (**4a**)	4-MeOC$_6$H$_4$ (**89f**)	99 (**148f**)	88
7	H (**4a**)	2-MeOC$_6$H$_4$ (**89g**)	96 (**148g**)	93
8	H (**4a**)	2-BrC$_6$H$_4$ (**89h**)	97 (**148h**)	96
9	H (**4a**)	3-BrC$_6$H$_4$ (**89i**)	99 (**148i**)	93
10	H (**4a**)	4-BrC$_6$H$_4$ (**89j**)	96 (**148j**)	92
11	H (**4a**)	2-FC$_6$H$_4$ (**89k**)	98 (**148k**)	96
12	H (**4a**)	3-F$_3$C C$_6$H$_4$ (**89l**)	99 (**148l**)	94
13	H (**4a**)	2-furyl (**89m**)	98 (**148m**)	88
14	H (**4a**)	1-naphthyl (**89n**)	95 (**148n**)	95
15	H (**4a**)	2-naphthyl (**89o**)	90 (**148o**)	93
16	H (**4a**)	*n*Bu (**89p**)	65 (**148p**)	70
17	Me (**4b**)	Ph (**89a**)	99 (**148q**)	94
18	MeO (**4c**)	Ph (**89a**)	99 (**148r**)	95
19	F (**4d**)	Ph (**89a**)	88 (**148s**)	94
20	Br (**4e**)	Ph (**89a**)	99 (**148t**)	94

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 amidoalkylation 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(II)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 *ee*s. Notably, various complexes


Re face (favored)
146

Fig. 6. The proposed coordination mode **146**.

Scheme 45. The AF-CA of indoles and various nitroalkenes.

catalyzed this reaction giving lower *ee*s 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 *ee*s 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(II)-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−CF$_3$−tryptophan and 4-CF$_3$-β-carboline in excellent enantioselectivity [74]. The generality of the AF-CA reaction was examined by using various indole derivatives and tri-fluoroethylidene malonates. Indole derivatives bearing both electron-donating and withdrawing groups were all appropriate substrates, manufacturing the corresponding CF$_3$-functionalized indoles in high chemical yields and moderate *ee*s. 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
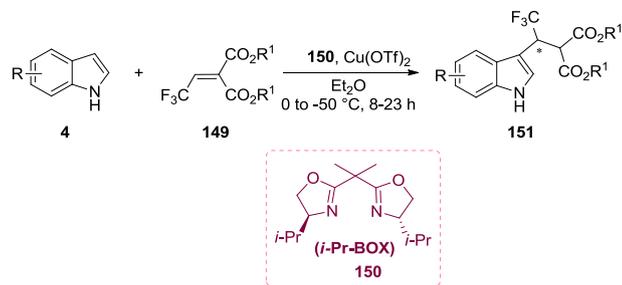
Scheme 46. Catalytic AF-C reactions of indoles **4** and trifluoroethylene malonates **149**.
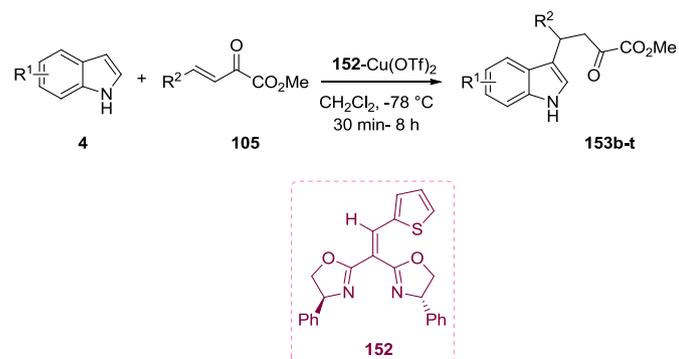
Table 23
Catalytic AF-C reactions of indoles **4** and trifluoroethylene malonates **149**.

Entry	R	R^1	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-O_2N	Bn	91 (**151m**)	75
14	5-O_2N	Me	98 (**151n**)	79
15	–	Bn	70 (**151o**)	16

7-position advanced with moderate *ees* (Scheme 46, Table 23) [74].

The facile and inexpensive chiral catalyst, heteroarylidene-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-CF_3Ph, 4-NO_2Ph substituents and indole having –CO_2Me 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

Scheme 47. Reactions of various indoles and β,γ-unsaturated α-ketoesters.

Table 24
Reactions of various indoles and β,γ-unsaturated α-ketoesters.

Entry	R^1	R^2	Yield (%)	ee (%)
1	H	2-ClC$_6$H$_4$	95 (**153b**)	>99
2	H	3-BrC$_6$H$_4$	99 (**153c**)	>99
3	H	2,4-Cl$_2$C$_6$H$_3$	95 (**153d**)	>99
4	H	4-FC$_6$H$_4$	99 (**153e**)	>99
5	H	4-BrC$_6$H$_4$	90 (**153f**)	99
6	H	4-NCC$_6$H$_4$	94 (**153g**)	>99
7	H	4-O$_2$NC$_6$H$_4$	88 (**153h**)	>99
8	H	4-F$_3$CC$_6$H$_4$	95 (**153i**)	>99
9	H	3-MeC$_6$H$_4$	89 (**153j**)	>99
10	H	4-MeC$_6$H$_4$	92 (**153k**)	>99
11	H	4-MeOC$_6$H$_4$	95 (**153l**)	94
12	5-Me	Ph	90 (**153m**)	>99
13	7-Me	Ph	92 (**153n**)	97
14	5-MeO	Ph	94 (**153o**)	99
15	5-Cl	Ph	90 (**153p**)	98
16	6-Cl	Ph	90 (**153q**)	>99
17	6-F	Ph	86 (**153r**)	>99
18	6-MeCO$_2$	Ph	81 (**153s**)	96
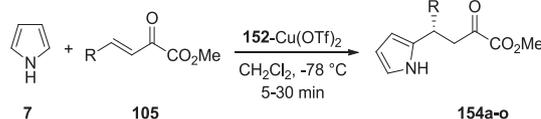
Scheme 48. Reactions of pyrrole with β,γ-unsaturated α-ketoesters.

examined. All reactions produced the pyrrole products **154** in 82—99% yields. In all reactions, excellent *ee*s 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-NO_2Ph, 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 heteroarylidene scaffold, and the excellent enantioselectivity provided from the well-defined chiral situation around the Cu center.

Table 25
Reactions of pyrrole with β,γ-unsaturated α-ketoesters.

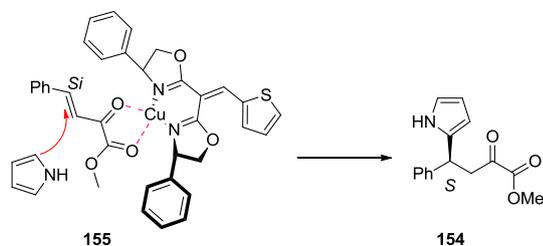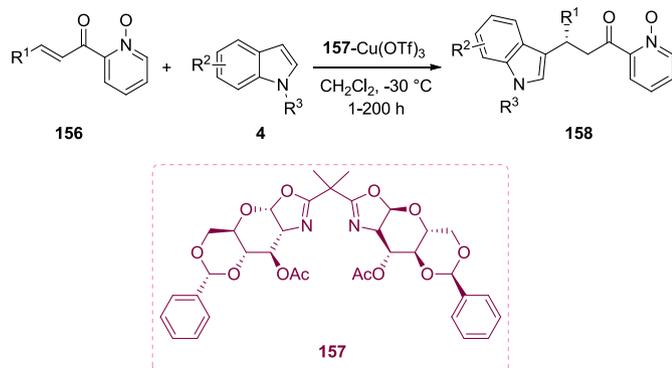| Entry	R	Yield (%)	ee (%)
1	Ph	95 (**154a**)	92
2	4-FC$_6$H$_4$	90 (**154b**)	92
3	4-ClC$_6$H$_4$	96 (**154c**)	90
4	4-BrC$_6$H$_4$	96 (**154d**)	90
5	4-NCC$_6$H$_4$	99 (**154e**)	91
6	4-O$_2$NC$_6$H$_4$	85 (**154f**)	86
7	4-F$_3$CC$_6$H$_4$	97 (**154g**)	88
8	2-ClC$_6$H$_4$	90 (**154h**)	85
9	3-BrC$_6$H$_4$	94 (**154i**)	90
10	3-NCC$_6$H$_4$	90 (**154j**)	88
11	3- O$_2$NC$_6$H$_4$	87 (**154k**)	89
12	4-MeC$_6$H$_4$	96 (**154l**)	91
13	4-MeOC$_6$H$_4$	82 (**154m**)	88
14	3-MeC$_6$H$_4$	90 (**154n**)	90
15	3-MeOC$_6$H$_4$	86 (**154o**)	92

Fig. 7. Proposed transition state for the AF-C reaction.

Both the phenyl substituent on the oxazoline ring, and the remote thiophene scaffold tethered to the double bond and the asymmetry of the current catalyst show a supportive effect on the observed high enantioselectivity [75].

The glucosamine obtained *gluco* BOX-Cu(II) [77] system has been known to be a distinctive catalytic complex for AF-CA of indoles and 2-enoylpyridine-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% [78]. 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-functionalized indole **158b** in 88% yield and 90% enantioselectivity. Also, 5-chloroindole generated the Michael adduct **158c** in 94% yield with 94%. Similar halogenated indole derivative, 4-MeO-indole gave **158d** in 94% yield and 85% enantioselectivity. In contrast, the alkylation reaction of **156a** and *N*-methylindole gave **158e** in 88% yield and fairly poor enantioselectivity. Also, 5-bromo-and 5-chloroindole derivatives treated well with **156b** to provide the desired products **158g** and **158h** with excellent enantioselectivity (Scheme 49, Table 26) [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 imidazoline-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

Table 26
AF-C reaction of various indoles and 2-enoylpyridine-*N*-oxides.

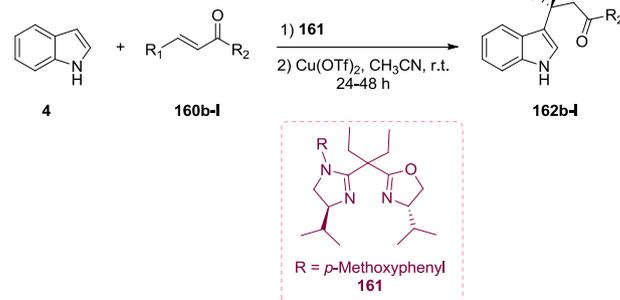| Entry	R^1	R^2, R^3	Yield (%)	ee (%)
1	4-ClC$_6$H$_5$ (**156a**)	H, H	94 (**158a**)	97
2	4-ClC$_6$H$_5$ (**156a**)	5-Br, H	88 (**158b**)	90
3	4-ClC$_6$H$_5$ (**156a**)	5-Cl, H	94 (**158c**)	94
4	4-ClC$_6$H$_5$ (**156a**)	5-MeO, Me	94 (**158d**)	85
5	4-ClC$_6$H$_5$ (**156a**)	H, H	88 (**158e**)	77
6	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-O$_2$NC$_6$H$_5$ (**156c**)	H, H	98 (**158j**)	96
11	4-MeC$_6$H$_5$ (**156d**)	H, H	87 (**158k**)	94
12	4-FC$_6$H$_5$ (**156e**)	H, H	94 (**158l**)	95
13	4-BrC$_6$H$_5$ (**156f**)	H, H	91 (**158m**)	92
1532	2-ClC$_6$H$_5$ (**156g**)	H, H	92 (**158n**)	99
15	2-FC$_6$H$_5$ (**156h**)	H, H	98 (**158o**)	94
16	2-ON$_2$C$_6$H$_5$ (**156i**)	H, H	96 (**158p**)	98
17	2-BrC$_6$H$_5$ (**156j**)	H, H	94 (**158q**)	96
18	3-O$_2$NC$_6$H$_5$ (**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	*t*Bu (**156n**)	H, H	65 (**158u**)	33
22	Cyclohexyl (**156o**)	H, H	Trace (**158v**)	n.d.
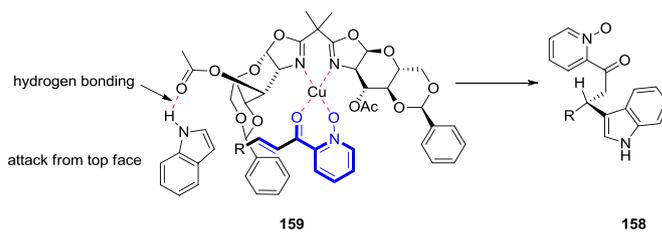
Fig. 8. A plausible transition state model for the AF-CA reaction of indole.

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 α,β-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 **4**, and different substrates **160b-l,** 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

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

Scheme 50. Highly AF-C reactions of indoles with α,β-unsaturated enones mediated by ligand **161**-Cu(OTf)$_2$.

Table 27
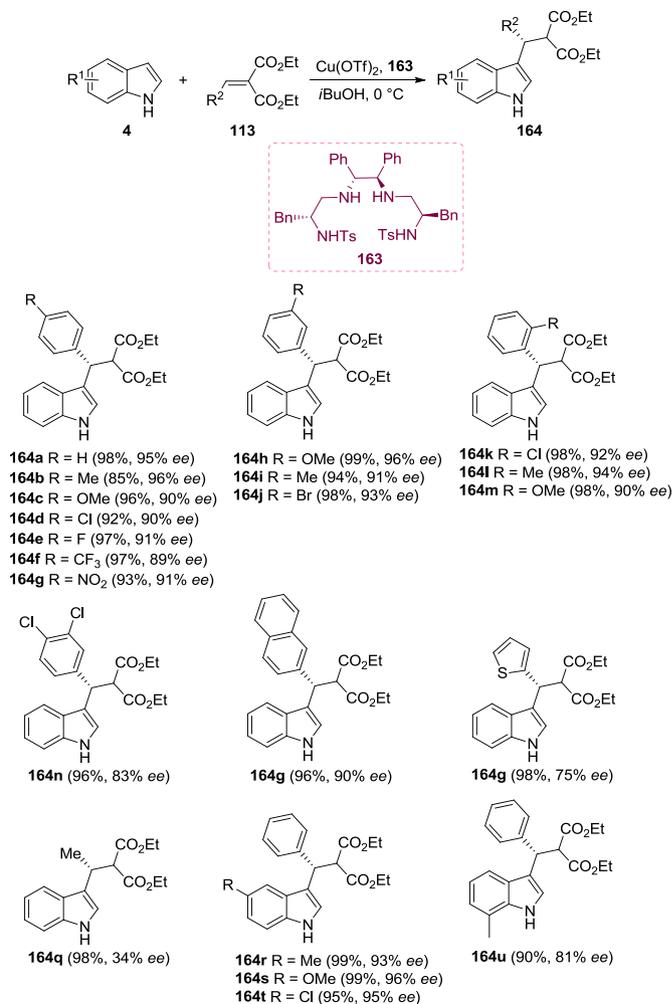Highly AF-C reactions of indoles with α,β-unsaturated mediated by ligand **161**-Cu(OTf)$_2$.

Entry	R^1,R^2	Yield (%)	ee (%)
1	p-ClPh, Ph	84	93.8 (S)
2	p-ClPh, Naphthyl	81	95.6 (S)
3	2,4,6-(CH$_3$)$_3$Ph, Ph	40	96.0 (S)
4	2,4,6-(CH$_3$)$_3$Ph, Napthy1	22	97.8 (S)
5	Tolyl, 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, Naphthy1	47	95.5 (S)
10	Thiophene, Ph	65	89.7 (R)
11	Ferrocene, Ph	8	87.7 (R)

should be mentioned that the lowest yield has been detected in substrate **160l** giving only 8% of the corresponding compound **162l** with 87% enantioselectivity through the most strict conditions, again the reason for this poor reactivity could be ascribed to the low solubility of product **160l** (Table 27) [80].

An extremely copper-mediated AF-CA reaction of indole derivatives and arylidene malonate derivatives with stable, simple and readily provided bis-sulfonamide diamine ligands has been achieved. The corresponding products have been formed with high yield and enantioselectivity [81]. Based on the optimization results, various 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 *ee*s, in spite of electron-withdrawing or donating substituents 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 *ee*s (**164n**-**p**). Inappropriately, once ethylidene malonate has been used, the reaction advanced with 98% yield and merely 34% enantioselectivity (**164q**). Excellent yields and *ee*s 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 **163**-copper(II) 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 R^2 of **163** turned the arylidene malonate in a fixed position. One phenyl substituent of (1R,2R)-1,2-diphenylethylenediamine 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 *ee*s 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)-

164a R = H (98%, 95% ee)
164b R = Me (85%, 96% ee)
164c R = OMe (96%, 90% ee)
164d R = Cl (92%, 90% ee)
164e R = F (97%, 91% ee)
164f R = CF$_3$ (97%, 89% ee)
164g R = NO$_2$ (93%, 91% ee)

164h R = OMe (99%, 96% ee)
164i R = Me (94%, 91% ee)
164j R = Br (98%, 93% ee)

164k R = Cl (98%, 92% ee)
164l R = Me (98%, 94% ee)
164m R = OMe (98%, 90% ee)

164n (96%, 83% ee)

164g (96%, 90% ee)

164g (98%, 75% ee)

164q (98%, 34% ee)

164r R = Me (99%, 93% ee)
164s R = OMe (99%, 96% ee)
**164t** R = Cl (95%, 95% ee)

164u (90%, 81% ee)

Scheme 51. Cu-mediated AF-CA of indoles **4** and various arylidene malonates **113**.
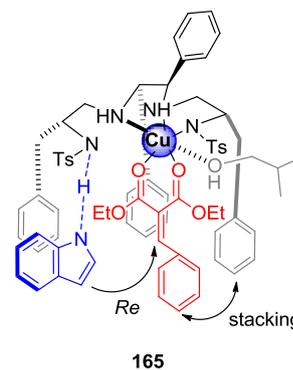
Fig. 9. Proposed transition state model of catalyst **163**-Cu(OTf)$_2$.

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

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-nitrosulfonamide and N-benzylidene-benzenesulfonamide 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 s-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.
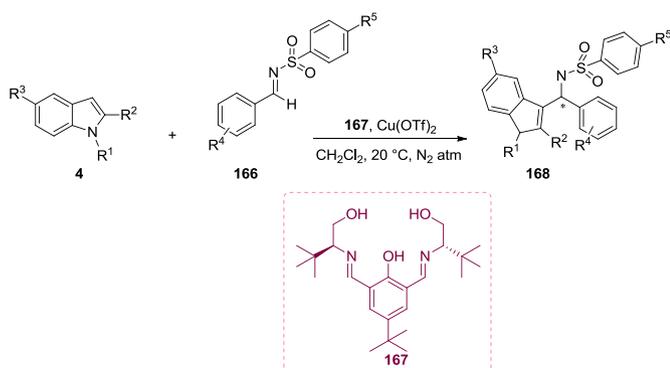
Table 28
The F-CA of various aldimines with indoles and substituted indoles.

Entry	R^1, R^2, R^3	R^4, R^5	Yield (%)	ee (%)
1	H, H, H	3-O$_2$N/Me	98 (168a)	97
2	H, H, H	4-O$_2$N/Me	98 (168b)	92
3	H, H, H	4-Br/Me	90 (168c)	95
4	H, H, H	4-NC/Me	86 (168d)	82
5	H, H, H	2-Cl/Me	75 (168e)	72
6	H, H, H	3-Cl/Me	85 (168f)	97
7	H, H, H	4-Cl/Me	89 (168g)	96
8	H, H, H	2-F$_3$C/Me	70 (168h)	65
9	H, H, H	4-F$_3$C/Me	85 (168i)	94
10	H, H, H	H/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-Br/O$_2$N	84 (168o)	96
16	H, H, MeO	3-O$_2$N/Me	89 (168p)	92
17	H, Me, H	3-O$_2$N/Me	78 (168q)	80
18	H, H, F	3-O$_2$N/Me	85 (168r)	89
19	Me, H, H	3-O$_2$N/Me	Trace	–

The substituent effect has been detected in the reaction rate; that is, the electron-donating methoxy-enhanced the reaction and the electron-withdrawing MeO$_2$C 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-k 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
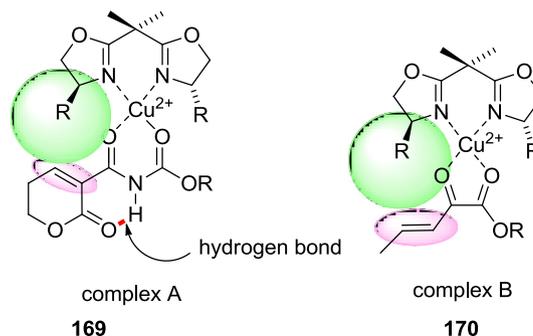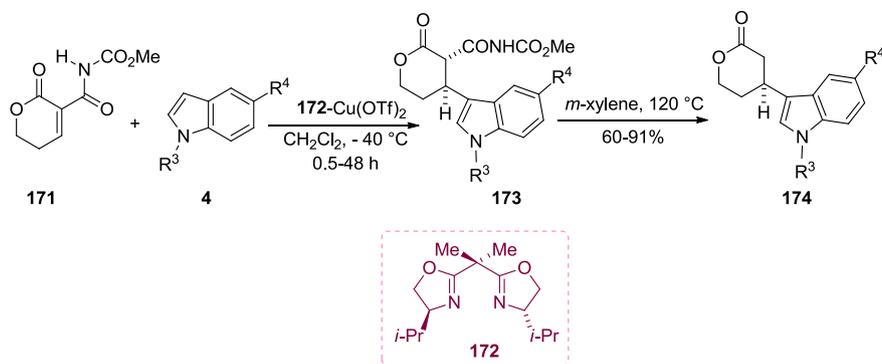

Scheme 52. The F-CA of various aldimines with indoles and substituted indoles.

Fig. 10. Suggested structures of systems 169 and 170.

Scheme 53. F–C reactions of α-alkylidene β-oxo imide **171** and derivatives **4**.

Table 29
F–C reactions of α-alkylidene β-oxo imide **171** and derivatives **4**.

Entry	R^3,R^4	Yield (%)	ee (%)
1	Me, H	80 (**173aa**)	93
2	H, H	87 (**173 ab**)	68
3	Bn, H	85 (**173ac**)	93
4	Ac, H	n.r.	–
5	Me, MeO	87 (**173ae**)	92
6	Me, MeO	88 (**173ae**)	95
7	Me, $MeCO_2$	70 (**173af**)	93
8	Me, Cl	86 (**173 ag**)	93

Scheme 54. Substrate scope for the reaction of α,β-unsaturated esters **175**.

Table 30
Substrate scope for the reaction of α,β-unsaturated esters **175**.

Entry	R^1, R^2	Ar	Yield (%)	ee (%)
1	Me, H	Ph (**135a**)	99 (**176aa**)	96
2	Me, H	4-BrC_6H_4 (**135b**)	92 (**176 ab**)	81 (*S*)
3	Me, H	4-FC_6H_4 (**135c**)	95 (**176ac**)	88
4	Me, H	2-ClC_6H_4 (**135d**)	98 (**176ad**)	55
5	Me, H	4-$MeOC_6H_4$ (**135e**)	98 (**176ae**)	93
6	Me, H	4-MeC_6H_4 (**135f**)	96 (**176af**)	92
7	Me, H	2-MeC_6H_4 (**135g**)	96 (**176ag**)	92
8	Me, H	3,4-$(MeO)_2C_6H_3$ (**135h**)	97 (**176ah**)	90
9	Me, H	2-naphthyl (**135i**)	98 (**176ai**)	90
10	Me, H	2-thienyl (**135j**)	98 (**176aj**)	91
11	Me, H	2-furyl (**135k**)	97 (**176ak**)	86
12	Et, H	Ph (**135a**)	93 (**176ba**)	91
13	*i*Pr, H	Ph (**135a**)	99 (**176ca**)	85
14	Bn, H	Ph (**135a**)	95 (**176da**)	79
15	Ph, H	Ph (**135a**)	99 (**176ea**)	88
16	Me, 5-MeO	Ph (**135a**)	99 (**176fa**)	84
17	Me, 6-Cl	Ph (**135a**)	98 (**176ga**)	82
18	Me, 7-Me	Ph (**135a**)	99 (**176ha**)	86

(Scheme 54, Table 30) [87].

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

Fig. 11. Proposed enantioselective induction model and the absolute configuration of **176 ab**.
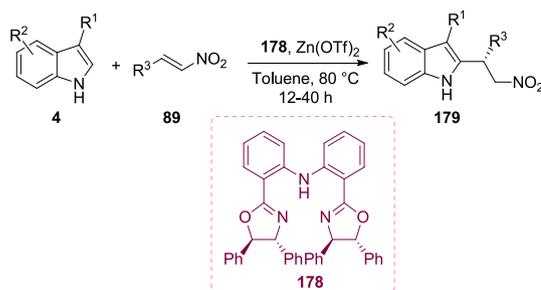
Scheme 55. Substrate scope for the F–C reaction of indoles and nitroalkenes.

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 *ee*s. 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 nitro-styrene **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 *ee*s. 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].
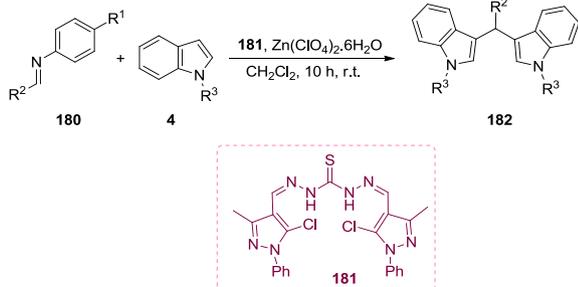
Table 31
Substrate scope for F—C the reaction of indoles and nitroalkenes.

Entry	R^1, R^2	R^3	Yield (%)	ee (%)
1	Me, H (**4a**)	Ph (**89a**)	97 (**179aa**)	92
2	Me, H (**4a**)	4-Me-C_6H_4 (**179 ab**)	97 (**179 ab**)	93
3	Me, H (**4a**)	4-MeO-C_6H_4 (**89c**)	99 (**179ac**)	90
4	Me, H (**4a**)	4-Cl—C_6H_4 (**89d**)	985 (**179ad**)	93
5	Me, H (**4a**)	4-Br—C_6H_4 (**89e**)	99 (**179ae**)	91 (*R*)
6	Me, H (**4a**)	3-MeO-C_6H_4 (**89f**)	97 (**179af**)	93
7	Me, H (**4a**)	2-MeO-C_6H_4 (**89g**)	99 (**179ag**)	91
8	Me, H (**4a**)	3,4-$(MeO)_2$—C_6H_3 (**89h**)	99 (**179ah**)	92
9	Me, H (**4a**)	1-naphthyl (**89i**)	98 (**179ai**)	91
10	Me, H (**4a**)	2-thienyl (**89j**)	95 (**179aj**)	92
11	Me, H (**4a**)	PhCh = CH (**89k**)	92 (**179ak**)	90
12	Et, H (**4b**)	Ph (**89a**)	96 (**179ba**)	94
13	Ph, H (**4e**)	Ph (**89a**)	96 (**179ea**)	96
14	Me, 5-MeO (**4f**)	Ph (**89a**)	92 (**179fa**)	91
15	Me, 7-Me (**4h**)	Ph (**89a**)	99 (**179ha**)	95
16	Me, 6-F (**4i**)	Ph (**89a**)	97 (**179ia**)	92

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 dithiocarbohydrazone Schiff base/ligand **181**/$Zn(ClO_4)_2 6H_2O$ 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 R^2. In all reactions, excellent yields have been provided, from 86% yield for the *para*-methoxy compound to 99% yield for the *p*-Br functionalized substrate, excepting *p*-N(CH_3)$_2$ and *o*-OH compounds (18% and 52% yield). Once R^2 was a hetero-aromatic group, high yields have been detected, even if the electron-withdrawing or -donating substituents were at the phenyl ring of R^1. Compared to the other groups of R^2, the hydroxyl imine derivatives afforded extremely poor yields (Scheme 56, Table 32) [88].

The chiral Lewis acid-mediated AF-CA of pyrrole derivatives with β-CF_3 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 *ee*s 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-

Table 32
The F—C reaction of indoles and various imines.

Entry	R^1	R^2	R^3	Yield (%)
1	H	Ph	H	97 (**182a**)
2	H	o-$O_2NC_6H_4$	H	97 (**182b**)
3	H	m-$O_2NC_6H_4$	H	99 (**182c**)
4	H	p-$O_2NC_6H_4$	H	92 (**182d**)
5	H	p-FC_6H_4	H	97 (**182r**)
6	H	p-ClC_6H_4	H	98 (**182f**)
7	H	p-BrC_6H_4	H	99 (**182g**)
8	H	p-MeC_6H_4	H	93 (**182h**)
9	H	p-$MeOC_6H_4$	H	86 (**182i**)
10	H	$2,4$-$Cl_2C_6H_3$	H	92 (**182j**)
11	H	p- $(Me)_2NC_6H_4$	H	18 (**182k**)
12	H	o-HOC_6H_4	H	52 (**182l**)
13	H	(pyrazole with N—Ph)	H	98 (**182m**)
14	F	(pyrazole with N—Ph)	H	99 (**182m**)
15	Cl	(pyrazole with N—Ph)	H	99 (**182m**)
16	Br	(pyrazole with N—Ph)	H	99 (**182m**)
17	O_2N	(pyrazole with N—Ph)	H	99 (**182m**)
18	Me	(pyrazole with N—Ph)	H	92 (**182m**)
19	Me	o-HOC_6H_4	H	- (**182l**)
20	Cl	o-HOC_6H_4	H	63 (**182l**)
21	O_2N	o-HOC_6H_4	H	76 (**182l**)
22	Me	3-MeO-4-HOC_6H_3	H	- (**182n**)
23	Cl	3-MeO-4-HOC_6H_3	H	67 (**182n**)
24	O_2N	3-MeO-4-HOC_6H_3	H	73 (**182n**)
25	H	Ph	CH_3	48 (**182o**)

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-dihydroindole 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
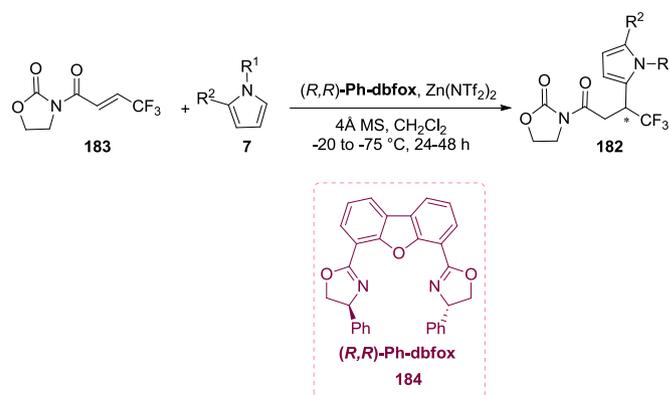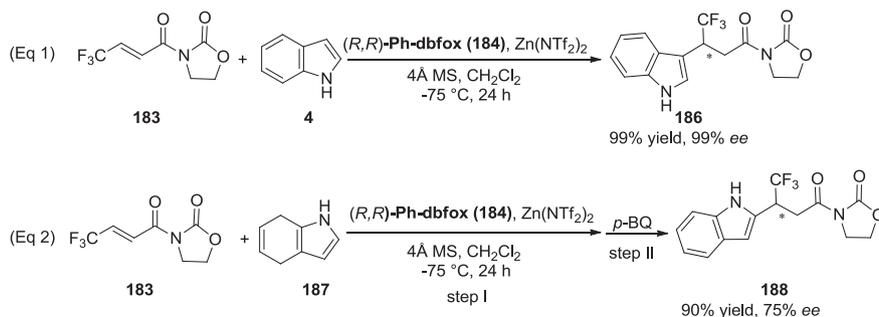

Scheme 56. The F—C reaction of indoles and various imines.

Scheme 57. AF-C reaction of β-CF_3 acrylates **183** and pyrrole derivatives.

Table 33
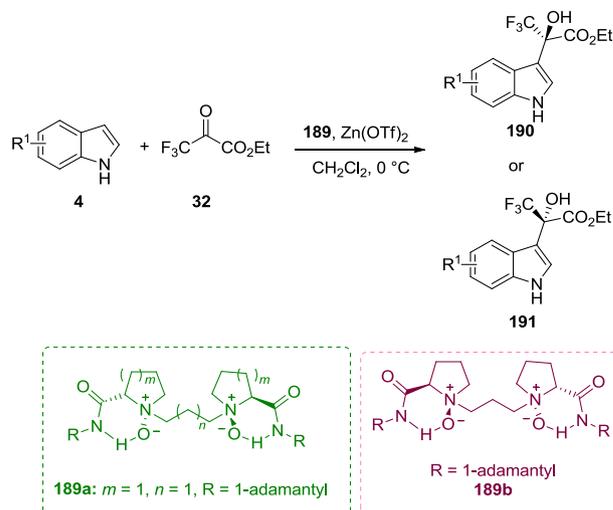AF-C reaction of β-CF$_3$ acrylates **183** and pyrrole derivatives.

Entry	R^1, R^2	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	*n*Pr, H (**7f**)	96 (**185f**)	95
6	*n*Bu, 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

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 trifluoro-pyruvate 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*s 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 *ee*s. 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 *ee*s and yields by employing the **189**-Zn(OTf)$_2$ catalytic system (Scheme 59, Table 34).
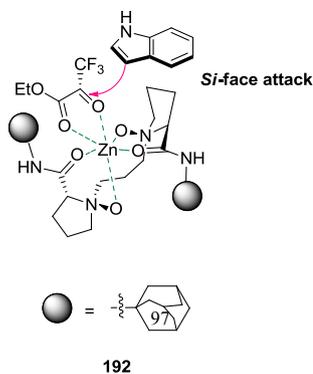

Scheme 59. F-CA of indole derivatives and ethyl trifluoropyruvate by *N,N'*-dioxide-zinc(II) systems.

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

Entry	R^1	Ligand	Yield (%)	*ee* (%)
1	H	**189a**	97 (**190a**)	90 (*R*)
	H	**189b**	97 (**191a**)	88 (*S*)
2	5-Me	**189a**	98 (**190b**)	74
	5-Me	**189b**	96 (**191b**)	77
3	6-Me	**189a**	93 (**190c**)	74
	6-Me	**189b**	98 (**191c**)	76
4	7-Me	**189a**	97 (**190d**)	94
	7-Me	**189b**	99 (**191d**)	95
5	7-Et	**189a**	99 (**190e**)	94
	7-Et	**189b**	96 (**191e**)	95
6	4-MeO	**189a**	97 (**190f**)	92
	4-MeO	**189b**	96 (**191f**)	94
7	5-MeO	**189a**	98 (**190g**)	71
	5-MeO	**189b**	98 (**191g**)	68
8	6-MeO	**189a**	97 (**190h**)	83
	6-MeO	**189b**	96 (**191h**)	84
9	5-F	**189a**	99 (**191i**)	93
	5-F	**189b**	99 (**191i**)	95
10	5-Cl	**189a**	99 (**190j**)	98
	5-Cl	**189b**	99 (**191j**)	96
11	5-Br	**189a**	97 (**190k**)	96
	5-Br	**189b**	99 (**191k**)	96
12	5-O$_2$N	**189a**	66 (**190**)	93
	5-O$_2$N	**189b**	75 (**191l**)	96

Scheme 58. AF-C reaction of β-CF$_3$ acrylates **183** and indoles.

Fig. 12. Proposed transition state **192**.

Scheme 61. AF-CA of 2-methoxyfuran **196** and functionalized nitroalkenes **89a-g** using ligand **193**.

Table 35
AF-CA of 2-methoxyfuran **196** and functionalized nitroalkenes **89a-g** using ligand **193**.
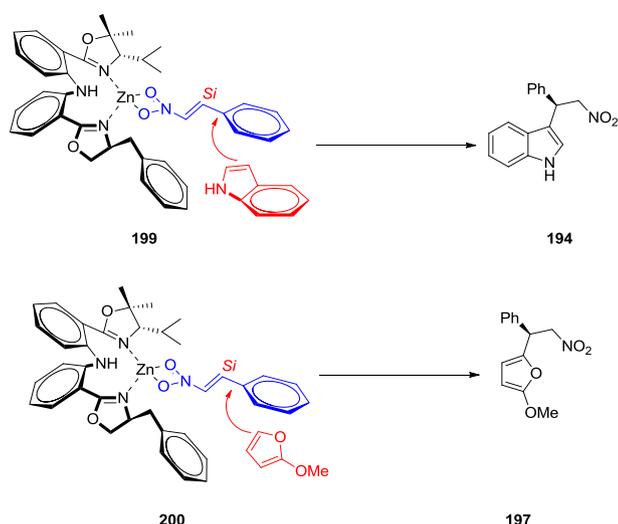
Entry	Ar	Yield (%)	*ee* (%)
1	Ph	88 (**198a**)	89
2	4-MeOC$_6$H$_4$	84 (**198b**)	92
3	4-BrC$_6$H$_4$	75 (**198c**)	93
4	4-MeC$_6$H$_4$	89 (**198d**)	92
5	2-furyl	70 (**198e**)	89
6	2-thienyl	68 (**198f**)	90
7	3-ClC$_6$H$_4$	83 (**198g**)	95

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 two six-membered chelate rings. In the meantime, bidentate ethyl trifluoropyruvate was linked to zinc (II) from the suitable side in this transition state, the *Re* 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 *Si* 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 oxazolinyl 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*s obtained for the products were found being in the range of 89—95% and chemical yields of 70—89%. Under optimal reaction conditions *meta*-chloro-functionalized nitrostyrene, afforded alkylated furan **198g** in 95% enantioselectivity while hetero-aromatic 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 *Si* 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*) [96]. 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*s ranging from 76: 24 to 92: 8. Remarkably, compound **122n** comprising 2,4-dichloro substituents afforded the corresponding product **202n** in 98%
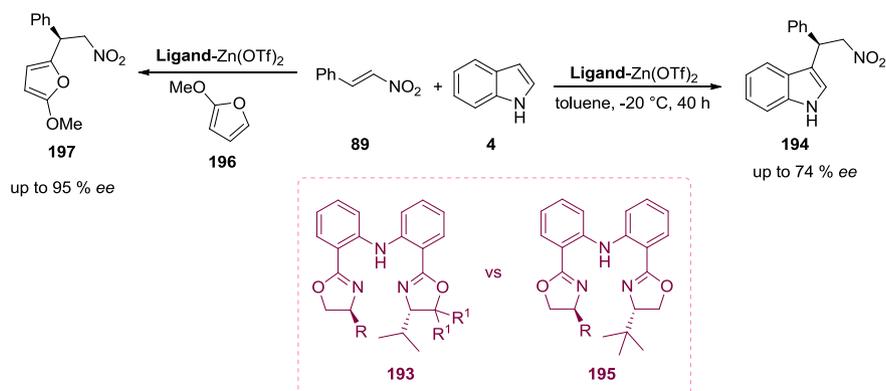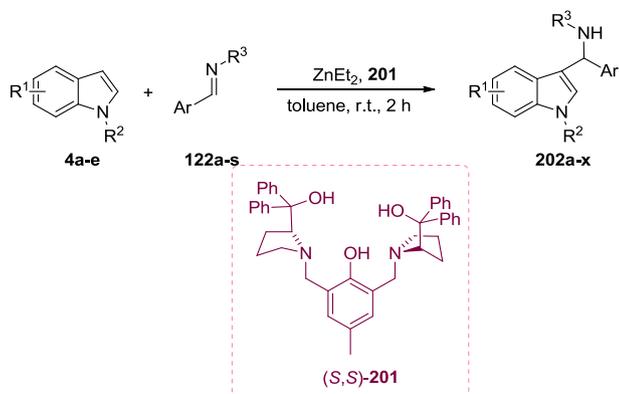

Scheme 60. The F-CA of indole and 2-methoxyfuran with different nitroalkene derivatives.

Scheme 62. Proposed transition states for the F-CA of indole **4** and 2-methoxyfuran **196**.
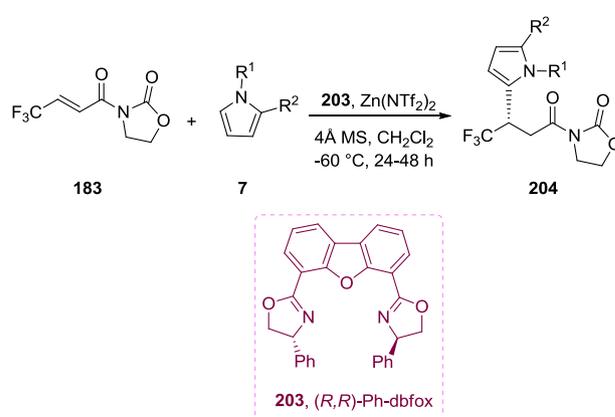
Table 36
The AF-C amidoalkylation of indoles and aryl aldimines catalyzed by Trost's bis-ProPhenol dinuclear zinc systems.

Entry	R^1, R^2 (Indoles)	R^3, Ar (Aldimines)	Yield (%)	*ee* (%)
1	H, H (**4a**)	Ts, Ph (**122a**)	95	92:8
2	H, H (**4a**)	Ts, *p*-FC$_6$H$_4$ (**122b**)	97	90:10
3	H, H (**4a**)	Ts, *p*-ClC$_6$H$_4$ (**122c**)	98	74:26
4	H, H (**4a**)	Ts, *p*-BrC$_6$H$_4$ (**122d**)	98	86:14 (*R*)
5	H, H (**4a**)	Ts, *p*-MeOC$_6$H$_4$ (**122e**)	90	82:8
6	H, H (**4a**)	Ts, *p*-MeC$_6$H$_4$ (**122f**)	98	78:22
7	H, H (**4a**)	Ts, *p*-F$_3$CC$_6$H$_4$ (**122g**)	98	94:6 (*R*)
8	H, H (**4a**)	Ts, *o*-ClC$_6$H$_4$ (**122h**)	98	92:8
9	H, H (**4a**)	Ts, *o*-FC$_6$H$_4$ (**122i**)	96	82:18
10	H, H (**4a**)	Ts, *o*-BrC$_6$H$_4$ (**122j**)	97	84:16
11	H, H (**4a**)	Ts, *o*-MeOC$_6$H$_4$ (**122k**)	98	90:10
12	H, H (**4a**)	Ts, *m*-MeC$_6$H$_4$ (**122l**)	92	88:12
13	H, H (**4a**)	Ts, *m*-ClC$_6$H$_4$ (**122m**)	98	76:24
14	H, H (**4a**)	Ts, 2,4-Cl$_2$C$_6$H$_3$ (**122n**)	98	95:5
15	H, H (**4a**)	Ts, 1-naphthyl (**122o**)	96	85:15
16	H, H (**4a**)	Ts, 2-naphthyl (**122p**)	90	78:22
17	H, H (**4a**)	Ts, thiophen-2-yl (**122q**)	85	81:19
18	5-Me, H (**4b**)	Ts, Ph (**122a**)	94	72:28
19	5-Br, H (**4c**)	Ts, Ph (**122a**)	98	70:30
20	7-Me, H (**4d**)	Ts, Ph (**122a**)	90	85:15
21	7-Me, H (**4d**)	Ts, *o*-ClC$_6$H$_4$ (**122h**)	91	87:13
25	H, H (**4a**)	B*sf*, Ph (**122r**)	87	85:15
53	H, H (**4a**)	*p*-ClC$_6$H$_4$, Ph (**122s**)	Trace	—
24	H, Me (**4e**)	Ts, Ph (**122a**)	Trace	—

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 *ee*s. 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-dibenzofurandiyl-2,2′-bis(4-phenyloxazoline)) [97]/Zn(NTf$_2$)$_2$ mediated AF-C reactions of β-CF$_3$ 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 −75 °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 65.1,4-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 approaching 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 nitrodiense has been thoroughly examined in the presence of diphenylamine-linked bis-(oxazoline)-zinc trifluoromethanesulfonate systems [99]. Satisfactory to good *ee*s have been provided using both types of substrates (up to 89% enantioselectivity for nitrodienes and up to 93% enantioselectivity for β-

Sheme 63. The AF-C amidoalkylation of indoles and aryl aldimines catalyzed by Trost's bis-ProPhenol dinuclear zinc systems.

Scheme 64. AF-C reaction of pyrroles **7b** and **183**.

Table 37
AF-C reaction of pyrroles **7b** and **183**.

Entry	R^1, R^2	Yield (%)	ee (%)
1	Me, H (**7a**)	96 (96) (**204a**)	96 (98)
2	H, H (**7b**)	96 (97) (**204b**)	98 (99)
3	Et, H (**7c**)	97 (96) (**204c**)	94 (96)
4	nPr, H (**7d**)	95 (96) (**204d**)	93 (95)
5	nBu, H (**7e**)	95 (95) (**204e**)	94 (95)
6	allyl, H (**7f**)	94 (90) (**204f**)	98 (99)
7	Bn, H (**7g**)	93 (**204g**)	85
8	Ph, H (**7h**)	94 (**204h**)	87
9	H, Me (**7i**)	96 (96) (**204i**)	88 (97)
10	H, Et (**7j**)	96 (98) (**204j**)	84 (97)
11	Me, Me (**7k**)	97 (97) (**204k**)	87 (94)
12	Me, Et (**7l**)	99 (99) (**204l**)	70 (88)
13	Me, Bn (**7m**)	95 (95) (**204m**)	66 (76)
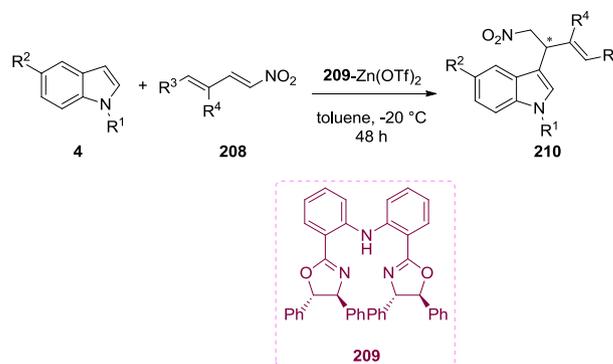
Scheme 66. AF-CA of indoles and nitrodienes.

nitrostyrenes) [100]. 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 enantiomeric purity. Indole derivatives containing various groups have been tested in the AF-CA reaction with nitrodiene **208**. 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 **210d** was increased to 91%, whereas the enantioselectivity reduced marginally. Once *N*-methylindole has been employed, the enantioselectivity reduced compared with the formerly reported outcome [101]. 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** reduced to 23%, however the enantioselectivity was preserved. Once the reaction temperature was raised to ambient temperature (25 °C), the desired 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 PhCH = CH and the ligand decreases the enantioselectivity in comparison with that of 1-[(*E*)-4-nitrobut-3-enyl]benzene (Scheme 66, Table 38) [101].

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 **212** 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. Additional aromatic substituents, for example naphthalene, was
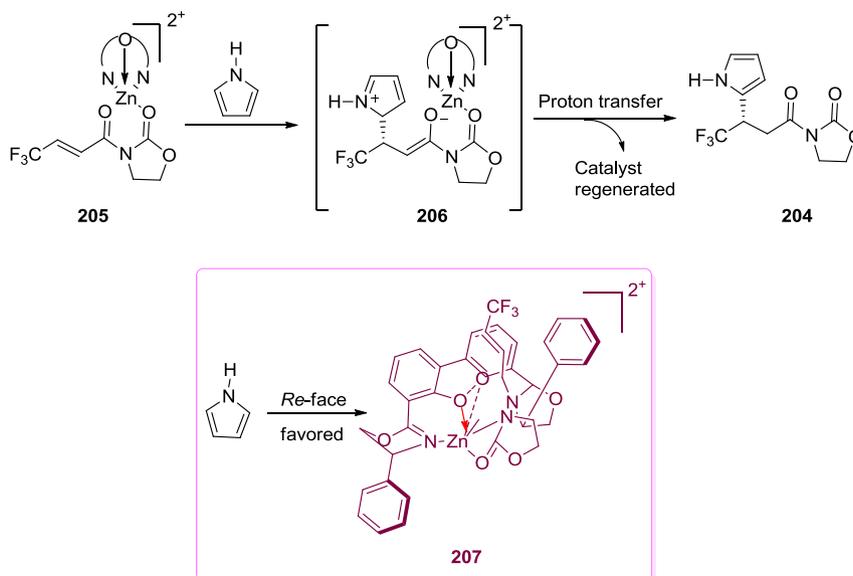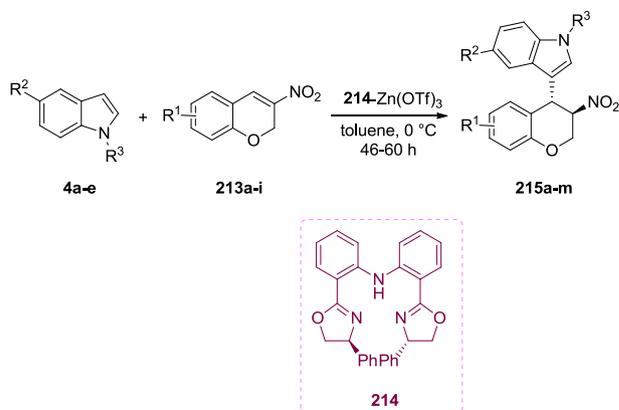

Scheme 65. Assumed catalytic cycle and probable model for the stereo-induction.

Table 38
AF-CA of indoles and nitrodienes.

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$_6$H$_4$, H	75 (**210i**)	89
10	H, H	4-MeOC$_6$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.

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

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-2*H*-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 *ee*s (up to 95%) [102]. Under optimal reaction conditions, the substrate scope the AF-CA reaction was examined by using various 3-nitro-2*H*-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 *de*s. As far as the enantioselectivities concern, the functionalized group on the phenyl of 3-nitro-2*H*-chromene, having both electron-donating and withdrawing substituents, resulted in moderate *ee*s, excepting for the substrate **213d**, with which the product has been provided in good *ee*. In addition, once electron-rich 5-methylindole

Table 40
AF-CA of indoles **4** and 3-nitro-2*H*-chromenes **213** catalyzed by **214**-zinc trifluoromethanesulfonate.

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

4b and 5-methoxyindole **4c** have been applied, the reaction advanced extremely easily with moderate yields, *ee*s and *de*s. 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 **215l** 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.

An extremely AF-CA of pyrrole with an extensive variety of simple nonchelating chalcones mediated by a chiral $(Zn_2EtL)_n$ (L =
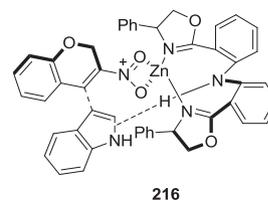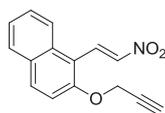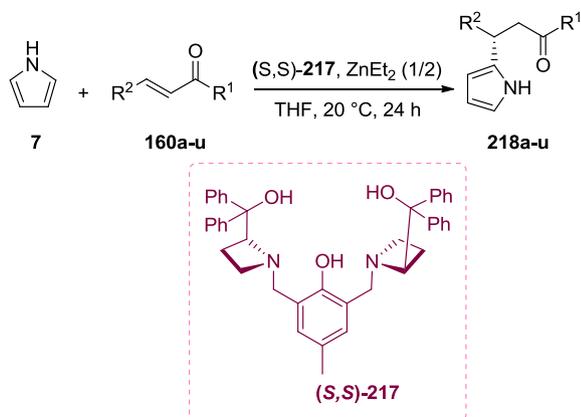
Table 39
AF-CA of indoles and nitroalkenes.

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 (*S*)
8	H, H	H, O$_2$N	99 (**212h**)	93
9	H, H	MeO, H	92 (**212i**)	68
10	H, H	EtO, H	91 (**212j**)	67
11	H, H	Cl, Cl	91 (**212k**)	89
12	H, H	Br, Br	85 (**212l**)	64
13	H, H	*t*Bu, *t*Bu	81 (**212m**)	36
14	H, H		99 (**212n**)	82

216

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 (Zn$_2$EtL)$_n$ system has been formed in situ by reacting the chiral ligand (S,S)-**217** with 2 equiv. of diethylzinc. A number of β-pyrrole-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 α,β-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 (R^1). The electronic influence or positions of the substrates on the aromatic ring (R^1) influenced the yields variously. The electron-donating substituent Me at the para position and the electron-withdrawing substituent Cl at the ortho position of the aromatic ring (R^1) resulted in a decline in yield. The corresponding products have been provided in high chemical yields and ees wherever the electron-withdrawing substituents of the aromatic ring (R^2) was present. The electron-donating substituent Me of the aromatic ring (R^2) did not change the ees; although, a decline in yield has been detected, particularly once it employed the meta position of the aromatic ring (R^2). 2-Naphthyl substrates treated easily with pyrrole at the optical reaction conditions providing the corresponding products with >99% enantioselectivity. The electron-withdrawing substituents of R^1 or R^2 were beneficial for the reaction. Thus, substrates having two electron-withdrawing substituents occupying R^1 and R^2 were provided for being examined. All of them treated with pyrrole in high yields and ees. Compound **160u** 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 R^1 or R^2 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 Zinc (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
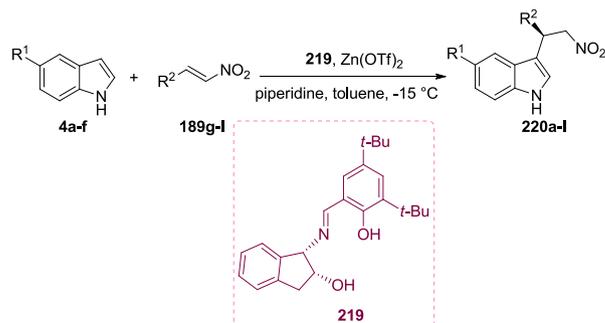
explored. The nitrostyrene having halogen (−Br, −Cl, −F) group at para position afforded desired products with moderate enantioselectivity. Electron-rich (-Me, -OMe) aromatic nitrostyrene at para position afforded the corresponding product with moderate enantioselectivity. Remarkably, a heterocyclic nitrostyrene derivative afforded moderate enantioselectivity as **220l**: 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 β-amino alcohols and 1,2,4,5-benzenetetracarboxylic acid through continuous elimination of H$_2$O. 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 ZnCl$_2$ 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	R^1	R^2	Yield (%)	ee (%)
1	Ph	Ph	99 (**218a**)	99
2	4-FC$_6$H$_4$	Ph	99 (**218b**)	99
3	4-ClC$_6$H$_4$	Ph	99 (**218c**)	98
4	4-BrC$_6$H$_4$	Ph	99 (**218d**)	99
5	4-MeC$_6$H$_4$	Ph	54 (**218e**)	98
6	3-ClC$_6$H$_4$	Ph	99 (**218f**)	98
7	3-BrC$_6$H$_4$	Ph	99 (**218g**)	99
8	2-ClC$_6$H$_4$	Ph	59 (**218h**)	99
9	Ph	4-ClC$_6$H$_4$	99 (**218i**)	98
10	Ph	4-BrC$_6$H$_4$	99 (**218j**)	>99
11	Ph	3-ClC$_6$H$_4$	99 (**218k**)	99
12	Ph	3-BrC$_6$H$_4$	99 (**218l**)	98
13	Ph	2-ClC$_6$H$_4$	99 (**218m**)	98
14	Ph	4-MeC$_6$H$_4$	94 (**218n**)	98
15	Ph	3-MeC$_6$H$_4$	67 (**218o**)	98
16	Ph	2-naphthyl	94 (**218p**)	>99
17	4-ClC$_6$H$_4$	2-ClC$_6$H$_4$	99 (**218q**)	98
18	4-FC$_6$H$_4$	3-BrC$_6$H$_4$	99 (**218r**)	99
19	4-BrC$_6$H$_4$	3-BrC$_6$H$_4$	99 (**218s**)	99
20	4-FC$_6$H$_4$	4-ClC$_6$H$_4$	99 (**218t**)	99
21	4-MeC$_6$H$_4$	4-ClC$_6$H$_4$	70 (**218u**)	99
22	4-MeOC$_6$H$_4$	Ph	—	—
23	Ph	4-MeOC$_6$H$_4$	—	—
24	Ph	iPr	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.

Table 42
AF-CA of indole derivatives and nitroalkenes.

Entry	R^1	R^2	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-BrC$_6$H$_4$	87 (**220g**)	69
8	H	4-ClC$_6$H$_4$	91 (**220h**)	76
9	H	4-FC$_6$H$_4$	93 (**220i**)	76
10	H	4-MeC$_6$H$_4$	88 (**220j**)	70
11	H	4-MeOC$_6$H$_4$	85 (**220k**)	72
12	H	furyl	94 (**2201**)	72
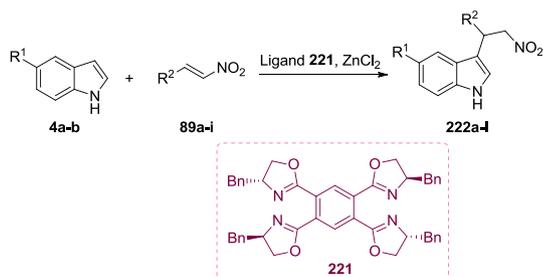
Scheme 71. AF-CA of indole derivatives and nitroalkenes.

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 β,γ-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

Scheme 72. AF-CA addition of indoles and β,γ-unsaturated α-ketoesters.

stereoselective AF-CA addition of β,γ-unsaturated α-ketoesters and indoles has been more explored. Initially, a variety of β,γ-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 β,γ-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-dihydro-oxazol-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 β,γ-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 β,γ-unsaturated α-ketoesters preferably from the *Si* face, providing principal synthesis

Table 43
AF-CA of indole derivatives and nitroalkenes.

Entry	R^1	R^2	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-MeOC$_6$H$_5$	98 (**222e**)	78
6	H	2-ClC$_6$H$_5$	85 (**222f**)	75
7	H	3-BrC$_6$H$_5$	87 (**222g**)	96
8	H	3-O$_2$NC$_6$H$_5$	95 (**222h**)	94
9	H	4-MeOC$_6$H$_5$	91 (**222i**)	90
10	H	4-ClC$_6$H$_5$	94 (**222j**)	95
11	H	2-furyl	89 (**222k**)	83
12	H	Me(CH$_2$)$_3$	91 (**222l**)	92

Table 44
AF-CA addition of indoles and β,γ-unsaturated α-ketoesters.

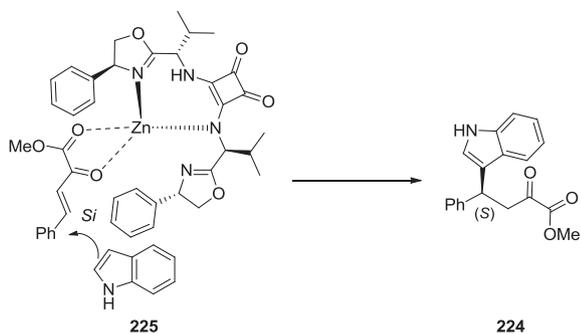| Entry	R^1, R^2	R^3	Yield (%)	ee (%)
1	H, H	Ph, Me (**13a**)	89 (**224a**)	93
2	H, H	4-ClC$_6$H$_4$, Me (**13b**)	98 (**224b**)	88
3	H, H	4-BrC$_6$H$_4$, Me (**13c**)	82 (**224c**)	81
4	H, H	4-FC$_6$H$_4$, Me (**13d**)	92 (**224d**)	89
5	H, H	4-MeOC$_6$H$_4$, Me (**13e**)	86 (**224e**)	89
6	H, H	4-MeC$_6$H$_4$, Me (**13f**)	98 (**224f**)	91
7	H, H	4-O$_2$NC$_6$H$_4$, Me (**13g**)	83 (**224g**)	79
8	H, H	2-O$_2$NC$_6$H$_4$, Me (**13h**)	74 (**224h**)	71
9	H, H	3,4-(MeO)$_2$C$_6$H$_3$, Me (**13i**)	92 (**224i**)	89
10	H, Me	Ph, Me (**13a**)	87 (**224j**)	32
11	5-Me, H	Ph, Me (**13a**)	86 (**224k**)	91
12	5-Cl, H	Ph, Me (**13a**)	87 (**224l**)	83
13	5-MeO, H	Ph, Me (**13a**)	87 (**224m**)	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

Fig. 14. The proposed transition state for stereochemical control.

Scheme 73. AF-CA reaction of indole 4 with nitroalkenes 89b-i using 226-Zn(OTf)$_2$ catalyst.

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-nitroalkenes 89b-i. Various samples have been took place applying ligand 226 and Zn(OTf)$_2$ in toluene. As demonstrated in Table 45, nitroalkenes 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 nitroalkenes having an electron-donating substituent on the aromatic ring had a faintly greater reaction rate than the treatments of nitrostyrenes having an electron-deficient substituent. While the greater *ee* of the corresponding products proposed that the electron-withdrawing substituent on the aromatic ring does not contain any important effect on the *ee*, when the treatment has been occurred at 15 mol % of 223-Zn(OTf)$_2$ at ambient temperature, a significant enhancement in the yield has been detected from 67%, 39%, 63%, and 75% to 79%, 51%, 77%, and 85%, respectively, while the *ee* significantly reduced to a wide range of 52–72% enantioselectivity (Scheme 73) [112].

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
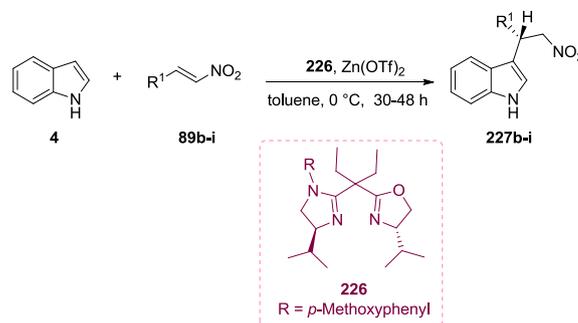
226-zinc (II) to make a four-membered intermediate 229, that endures a nucleophilic addition reaction of indole (from the available *Si* face) [113] to give the AF-CA product 230. Then, H-transfer 231 followed by fragmentation, generating an adduct along with recreation of the oxazoline-imidazoline-Zn(II) catalyst 228 [112].

A direct AF-CA reaction of various indole derivatives and ethyl 2-(4-methoxyphenylimino)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 *ee*s. 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 raise 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 *ee*s (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

Table 45
AF-CA reaction of indole 4 with nitroalkenes 89b-i using 226-Zn(OTf)$_2$ catalyst.

Entry	R^1	Yield (%)	*ee* (%)
1	4-MePh	89 (227b)	96.6 (S)
2	4-MeOPh	82 (227c)	97.2 (S)
3	4-ClPh	87 (227d)	98.5 (S)
4	4-BrPh	67 (227e)	96.1 (S)
5	4-BrPh	79 (227e)	72.1 (S)
6	4-O$_2$NPh	39 (227f)	94.9 (S)
7	4-O$_2$NPh	51 (227f)	66.4 (S)
8	2,4-Cl$_2$Ph	81 (227g)	98.8 (R)
9	2,6-Cl$_2$Ph	63 (227h)	97.6 (R)
10	2,6-Cl$_2$Ph	77 (227h)	52.4 (R)
11	2-ferrocene	75 (227i)	96.9 (R)
12	2-ferrocene	85 (227i)	54.8 (R)
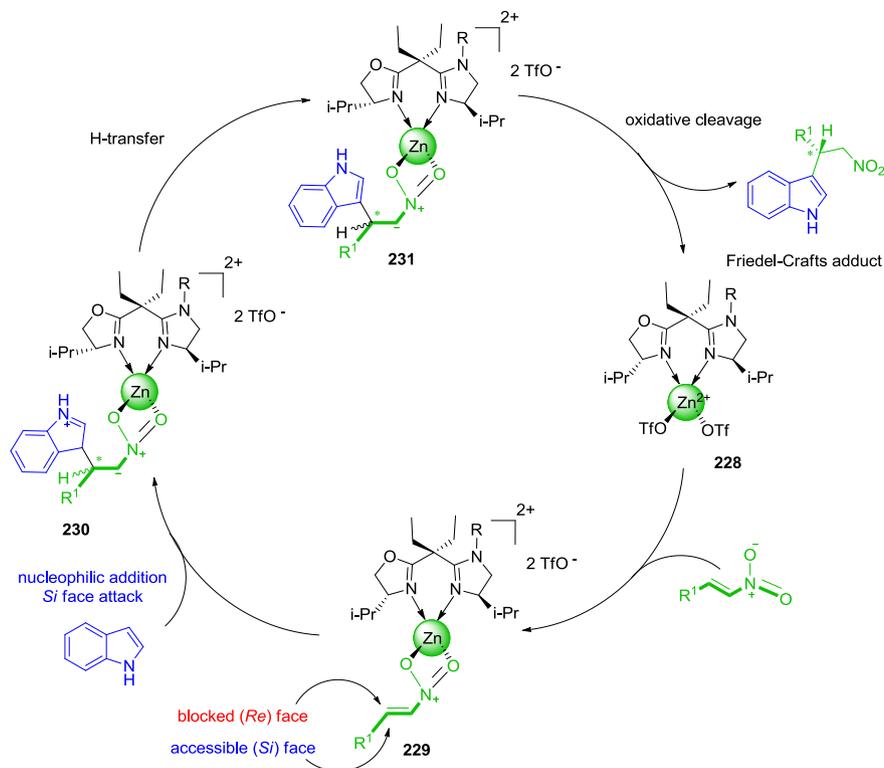
Scheme 74. Proposed catalytic cycle for the alkylation of indole with nitroalkene.
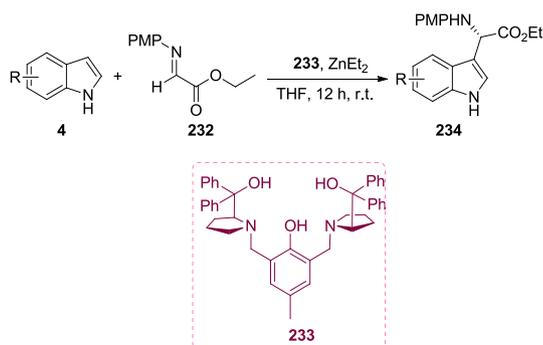
Scheme 75. Catalytic AF-CA of various indoles **4** and imine **232**.

Table 46
Catalytic AF-CA of various indoles **4** 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-BocO	64	91
7	4-AcO	72	91
8	4-Ph	48	54
9	5-O_2N	81	30
10	5-F	77	86
11	5Cl	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- $MeCO_2$	68	66
20	2-Me	88	51
21	7-Me	36	12
22	7-Cl	trace	–

between intermediate **238** and approaching indole **4** releases the product **234** and reinitiates the catalytic cycle (Scheme 76) [114].

2.5. Scandium

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 **239** and functionalized phenol derivatives **240** has been examined. First, the influence of the ester substituent of (*E*)-4-oxo-4-arylbutenoates has been tested for the AF-CA reaction of phenol. The ester groups had slight effect on the *ee*, and slightly reduced yields have been provided for sterically hindered ester substituent. Once the electron-donating substituent on the phenol has been varied, the reactions were performed easily with moderate *ee*s 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 enantiose-lectivity. It should be mentioned that the 3,4-dimethoxy-functionalized (*E*)-ethyl 4-oxo-4-arylbutenoate **239j** gave high
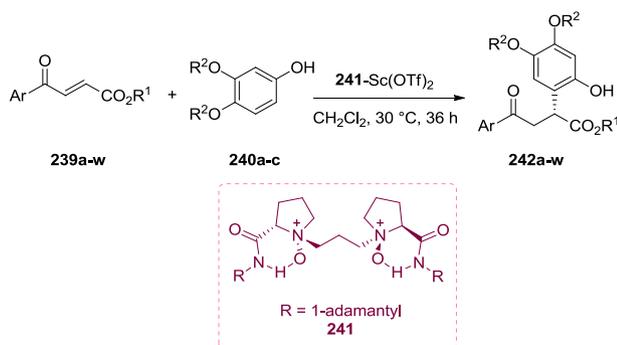
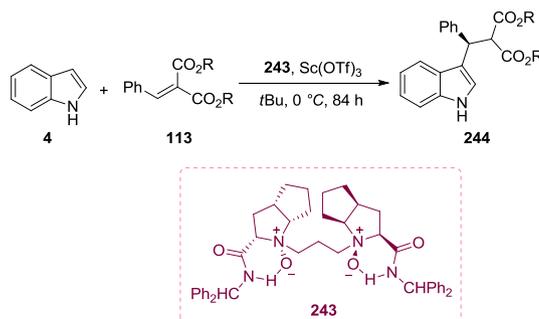**Scheme 76.** Proposed catalytic cycle for AF-C reaction.

Table 47
AF-CA reaction of activated phenols and (*E*)-4-oxo-4-arylbutenoate derivatives using *N,N′*-dioxide-Sc (III) system.

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	*i*Pr	Me	78 (**242c**)	92 (*R*)
4	Ph	*t*Bu	Me	87 (**242d**)	95 (*R*)
5	Ph	Bn	Me	96 (**242e**)	92 (*R*)
6	Ph	Et	Et	93 (**242f**)	91 (*R*)
7	Ph	Et	*i*Pr	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 β-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 *ee*s. The *ee* of this reaction was insensitive to the electronic and steric properties of meta-groups on the aromatic ring in arylidene malonate, that was different from the reactions which were catalyzed by complexes of chiral Cu(II)-oxazoline. Moreover, the *para*-functionalized arylidene malonates were found being significant for the reaction giving moderate *ee*s, for the products, although the *ortho*-functionalized one demonstrated a decreased in *ee*, that could be related to the steric hindrance effects of *ortho*-position. Remarkably, the reaction could take longer time for completion in comparison of the reaction

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 **242s** has been demonstrated to be *R* (Scheme 77, Table 47) [115].

N,N′-dioxide−Sc(III) systems were showed to be significant chiral Lewis acid catalysts [116]. The chiral *N,N′*-dioxide **243** obtained from ʟ-ramiprol acid and diphenylmethyl amine afforded the desired product with the uppermost *ee*s [117]. An extremely significant AF-CA of indole derivatives and alkylidene malonates was achieved by using chiral *N,N′*-dioxide **243**-Sc(III) system as the catalyst, providing the desired products in excellent yields and high *ee*s (up to 99% yield and 95% enantioselectivity). The product **244a** has been simply transformed to various exciting compounds, for instance tryptamine derivatives, β-carboline and indolepropionic

Scheme 77. AF-CA reaction of activated phenols and (*E*)-4-oxo-4-arylbutenoate derivatives using *N,N′*-dioxide-Sc (III) system.

Scheme 78. Enantioselective AF-CA of indole derivatives and alkylidene malonates.

Table 48
Enantioselective AF-CA of indole derivatives and alkylidene malonates.

Entry	R	Yield (%)	ee (%)
1	Me	12	64
2	Et	46	81 (R)
3	nPr	20	80
4	iPr	6	83
5	tBu	4	3
6	PhCH	59	71
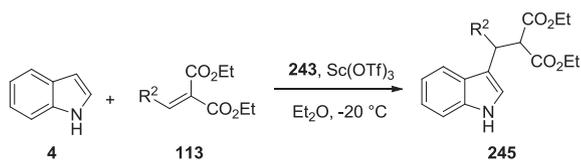
**Scheme 79.** Catalytic AF-C reaction of indole **4** and alkylidene malonates **113**.

of condensed-ring, heterocyclic and difunctionalized arylidene malonates wich gives moderate to high *ee*s for the corresponding products. Unfortunately, merely satisfactory yield and enantioselectivity were obtained for the cyclohexylidene malonate (Scheme 79, Table 49) [117].

Both the oxygens of *N*-oxide and carbonyl oxygens linked with scandium (III) in a tetradentate manner to make a suitable catalyst. A model for the transition state has been suggested. In this proposed model for the transition state, scandium (III) linked in a hexadentate mode with **243** and alkylidene malonate. The *Re* face of the alkylidene malonate has been blocked with the bulky diphenylmethyl substituent. Therefore, indole attacks from the *Si* face for the formation of the desired product with *R* configuration. The transition state can assist to elucidate the performance, which merely racemic compound with good yield is obtained once *N,N'*-dioxide **243** is used as the precursor (Fig. 15) [117].

As depicted in Scheme 80, a catalytic cycle was also proposed to elucidate the reaction mechanism. First, the introduction of *t*-BuOH to the mixture of **243** and Sc(OTf)₃ generates the catalytically active species **246**. After ligands exchange, the alkylidene malonate is introduced into the chiral environment to give the activated substrate-catalyst complex **247**. Then, indole attack the *Si* face of

Table 49
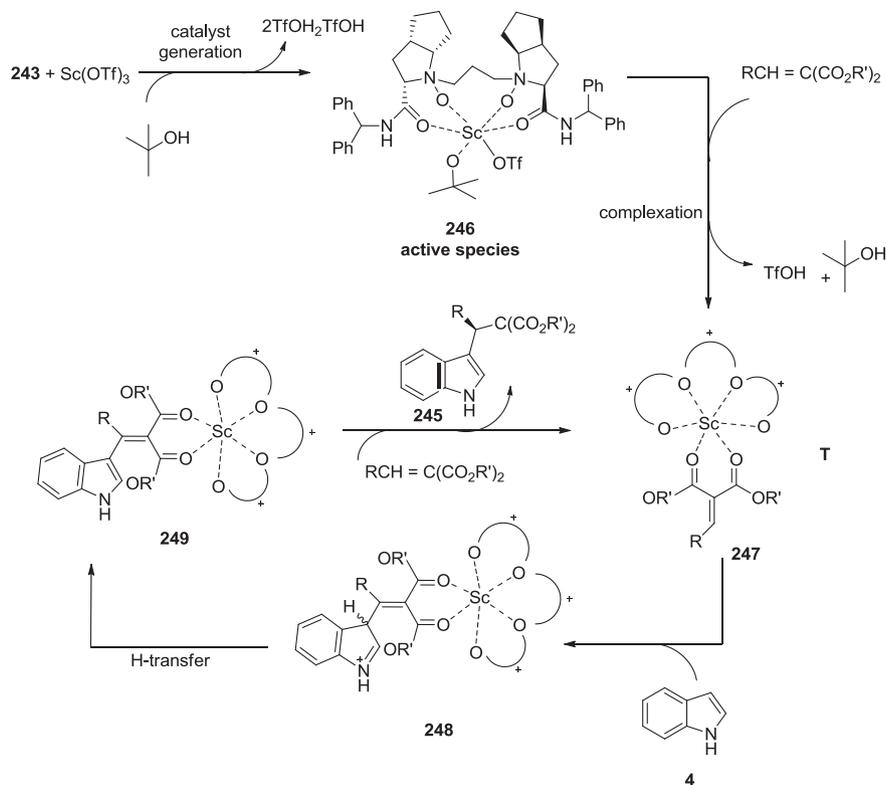Catalytic AF-C reaction of indole **4** and alkylidene malonates **113**.

Entry	R²	Yield (%)	ee (%)
1	Ph	94 (**245a**)	90 (R)
2	3-MeC₆H₄	84 (**245b**)	90
3	3-MeOC₆H₄	59 (**245c**)	92
4	3-PhOC₆H₄	90 (**245d**)	93
5	3-F₃CC₆H₄	90 (**245e**)	92
6	3-O₂NC₆H₄	73 (**245f**)	82
7	3-BrC₆H₄	97 (**245g**)	92
8	3-ClC₆H₄	84 (**245h**)	87
9	4-FC₆H₄	98 (**245i**)	83
10	4-BrC₆H₄	97 (**245j**)	80
11	4-O₂NC₆H₄	74 (**245k**)	71
12	4-ClC₆H₄	92 (**245l**)	80
13	4-NCC₆H₄	55 (**245m**)	75
14	4-F₃CC₆H₄	87 (**245n**)	82
15	4-MeC₆H₄	97 (**245o**)	80
16	2-ClC₆H₄	71 (**245p**)	62
17	3-PhO-4-FC₆H₃	77 (**245q**)	88
18	3,4-Cl₂C₆H₃	92 (**245r**)	83
19	2-naphthyl	72 (**245s**)	80
20	2-thienyl	83 (**245t**)	71
21	cyclohexane	57 (**245u**)	43
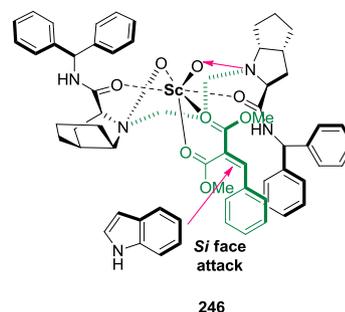
Fig. 15. Proposed transition state **246**.

the alkylidene malonate followed by the H-transfer and decomplexation of the desired product from the central metal to regenerate the intermediate **247**. The catalytic cycle is thus completed [117].

The AF-C reaction of methyl (*E*)-2-oxo-4-aryl-3-butenoates **239a-c** and activated benzenes **250a-d** was significantly mediated using the Sc(OTf)₃ system of (4′*S*,5′*S*)-2,6-bis[4'-(triisopropylsilyl) oxymethyl-5′-phenyl-1′,3′-oxazolin-2′-yl]pyridine (pybox **251**) [119]. The 4,4-diaryl-2-oxo-butyric acid methyl ester derivatives **252** were frequently provided in moderate yields and the high enantioselectivity [120]. Remarkably, the sense of the stereo induction 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 initial simple model to examine the application of the catalyst was the reaction of **239** and 1,3,5-trimethoxybenzene **250a**. Preliminarily, the reaction of methyl (*E*)-2-oxo-4-phenyl-3-butenoate **239a** with **250a** was accomplished with Sc(OTf)₃ without a chiral ligand in dichloromethane at −50 °C, and the yield of **252aa** was approximately quantitative. Next, the identical reaction has been performed both at −50 °C and −20 °C using 10% mol of [(TIPS-pybox)/ scandium(III) triflate] and 3 Å molecular sieves (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 enantioselectivity 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 **239b,c** and **250a** have been accomplished in the presence of either scandium (III) or [(**251**)/scandium(III) triflate]. Even if the reactions at −50 °C afford poor yields (56 and 20% for **239b** and **239c**, respectively), the *ee*s of the reaction were found being again high (*ee* >95%). At −20 °C, the enantioselectivity 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) triflate system were achieved which endured various substrates. The reaction advances in good to high yields and excellent *ee*s 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].

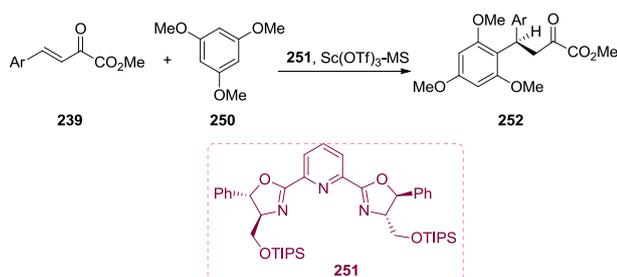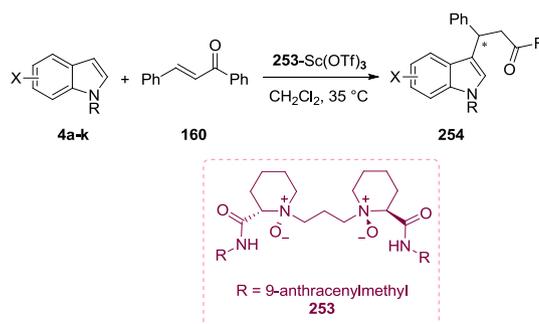**Scheme 80.** A proposed catalytic cycle to elucidate the reaction mechanism.

Scheme 81. Reaction of methyl (*E*)-2-oxo-4-aryl-3-butenoates **239** with 1,3,5 trimethoxybenzene **250**.

Scheme 82. Catalytic AF-C reaction of indole derivatives and chalcone **160**.

Table 50
F−C reaction of methyl (*E*)-2-oxo-4-aryl-3-butenoates **239a-c** and **250** in CH$_2$Cl$_2$ at −50 °C using 10 mol % catalyst.

Entry	1	Catalyst	T (C)	Time	Yield (%)	ee (%)
1	Ph (**239a**)	Sc(OTf)$_3$	−50	1 h	90 (**252aa**)	−
2	Ph (**239a**)	[**251**, Sc(OTf)$_3$]	−50	24 h	92 (**252aa**)	97 (+)
3	Ph (**239a**)	[**251**, Sc(OTf)$_3$]	−20	5 h	97 (**252aa**)	>99 (+)
4	4-BrC$_6$H$_4$ (**239b**)	Sc(OTf)$_3$	−50	1 h	70 (**252ba**)	−
5	4-BrC$_6$H$_4$ (**239b**)	[**251**, Sc(OTf)$_3$]	−50	24 h	56 (**252ba**)	99 (+)
6	4-BrC$_6$H$_4$ (**239b**)	[**251**, Sc(OTf)$_3$]	−20	7 h	86 (**252ba**)	89 (+)
7	4-O$_2$NC$_6$H$_4$ (**239c**)	Sc(OTf)$_3$	−20	2 h	84 (**252ca**)	−
8	4-O$_2$NC$_6$H$_4$ (**239c**)	[**251**, Sc(OTf)$_3$]	−50	7 d	20 (**252ca**)	96 (+)
9	4-O$_2$NC$_6$H$_4$ (**239c**)	[**251**, Sc(OTf)$_3$]	−20	2 d	85 (**252ac**)	87 (+)

Table 51
Catalytic AF-C reaction of indole derivatives and chalcone **160**.

Entry	Indole	Time (h)	Yield (%)	ee (%)
1	H, H (**4a**)	28	99 (**254aa**)	92
2	7-Me, H (**4b**)	40	99 (**254ba**)	90
3	7-Et, H (**4c**)	44	92 (**254ca**)	92
4	5-Me, H (**4d**)	44 (60)	99 (89) (**254da**)	89 (88)
5	5-MeO, H (**4e**)	44	94 (**254ea**)	90
6	6-MeO, H (**4f**)	40 (55)	99 (81) (**254fa**)	85 (85)
7	2-Me, H (**4g**)	44 (48)	99 (84) (**254ga**)	81 (81)
8	5-Br, H (**4h**)	40	50 (**254ha**)	90
9	5-Cl, H (**4i**)	40	78 (**254ia**)	90
10	5-F, H (**4j**)	44	79 (**254ja**)	86
11	H, Me (**4k**)	44	74 (**254ka**)	74

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
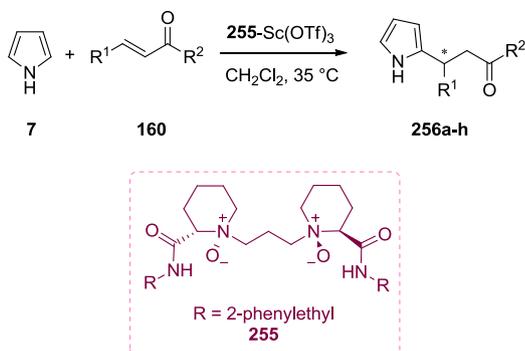
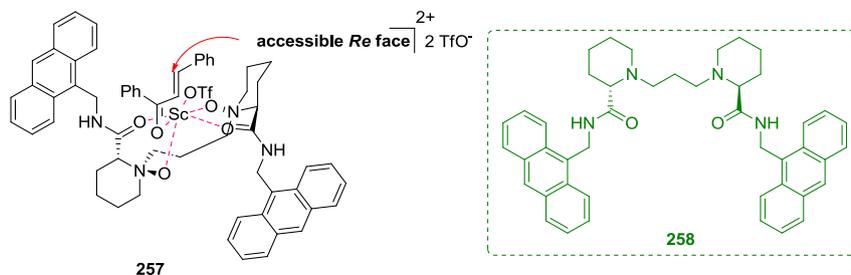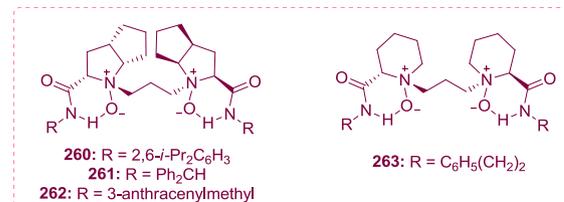**Scheme 83.** Catalytic AF-C reaction of pyrrole **7** and enones **160**.

Table 52
Catalytic AF-C reaction of pyrrole **7** and enones **160**.

Entry	R^1	R^2	Yield (%)	ee (%)
1	Ph	Ph	73 (**256a**)	92
2	4-BrC$_6$H$_4$	Ph	78 (**256b**)	92
3	4-MeC$_6$H$_4$	Ph	55 (**256c**)	92
4	4-Cl	Ph	48 (**256d**)	92
5	4-ClC$_6$H$_4$	Ph	80 (**256e**)	90
6	Ph	4-FC$_6$H$_4$	75 (**256f**)	92
7	Ph	4-MeC$_6$H$_4$	46 (**256g**)	92
8	Me	Ph	46 (**256h**)	74

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,N′*-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-Indolyl(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)$_3$ **263** mediated enantioselective reactions of chalcone derivatives [121] Controlled reversal of enantioselectivity by samarium(III) trifluoromethanesulfonate/AgAsF$_6$ and *N,N′*-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].
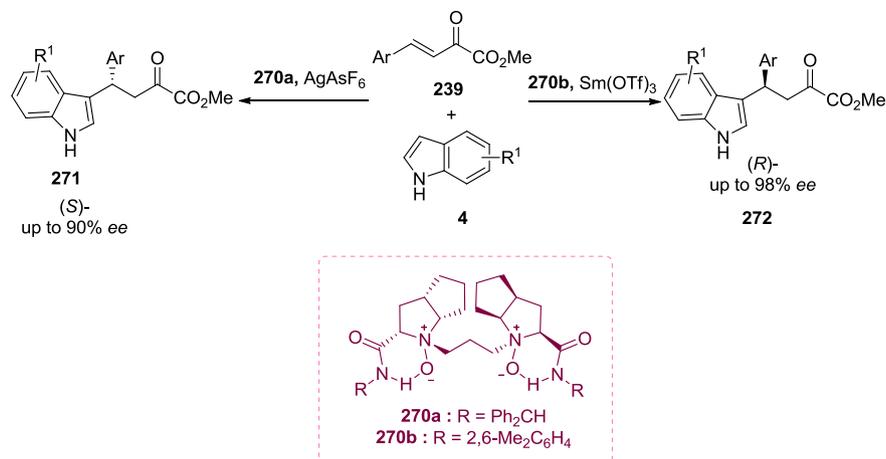

**Scheme 84.** AF-C reaction.

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)−Me$_2$-CATPHOS [124]. The catalysts have been provided spontaneously by the reaction between [MCl$_2$(cycloocta-1,5-diene)] [125] (M = Pd, Pt) and either (S) −Me$_2$-CATPHOS or (S)-BINAP in CH$_2$Cl$_2$ to prepare [MCl$_2$(diphosphine)], that was successively transformed into the desired Lewis acid [M(diphosphine)][OTf]$_2$ *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].


Fig. 16. Proposed transition-state **257**.

Scheme 85. Reversal of the enantioselectivity in F–C reaction.
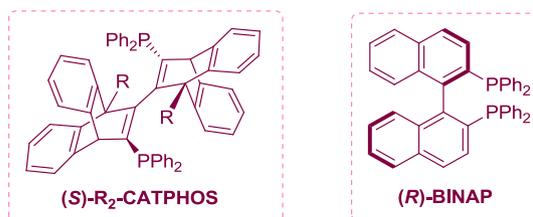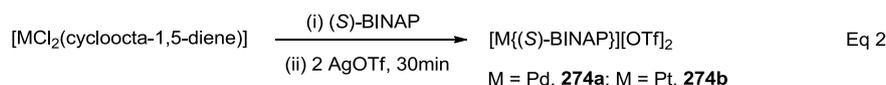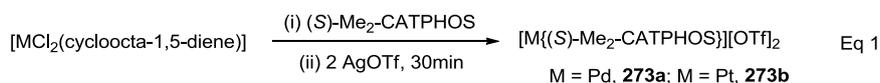
Scheme 86. Lewis acids based on Pt and Pd.

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 [129] 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-vinyltetrahydrocarbazole 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) [130].

Fascinatingly, intramolecular cyclization of **280a**, (S)-3,5-*t*Bu-4-MeO-MeOBIPHEP in the presence of **276l** gave synthetically
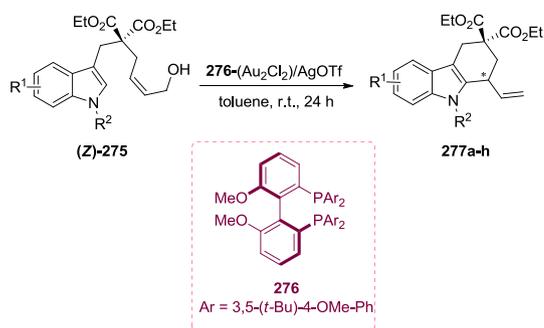

Scheme 87. The intramolecular asymmetric allylic alkylation of (Z)-**275**.

valuable compound **281a** (yield = 71%, ee = 80%) while (S)-xylyl-phanephos **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	R^1	R^2	Yield (%)	ee (%)
1	5-Br	H	60 (**277a**)	86
2	5-Me	H	68 (**277b**)	92
3	5-MeO	H	55 (**277c**)	96
4	7-Me	H	91 (**277d**)	83
5	5-BnO	H	78 (**277e**)	80
6	5-Cl	H	52 (**277f**)	85
7	H	H	74 (**277g**)	85
8	H	H	53 (**277h**)	92
9	H	Me	0 (**277i**)	–
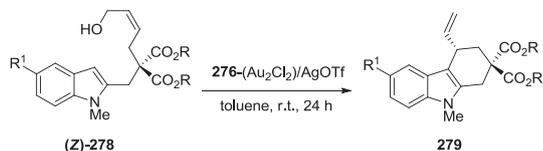
Scheme 88. Catalytic asymmetric intramolecular F-CA reactions for the synthesis of 4-vinyl tetrahydrocarbazoles **279**.

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

Entry	R, R^1	Yield (%)	ee (%)
1	Et, H (**278a**)	79 (**279a**)	86
2	tBu, H (**278b**)	80 (**279b**)	80
3	Me, H (**278c**)	87 (**279c**)	74
4	Et, MeO (**278d**)	55 (**279d**)	83
5	Et, Me (**278e**)	87 (**279e**)	80

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
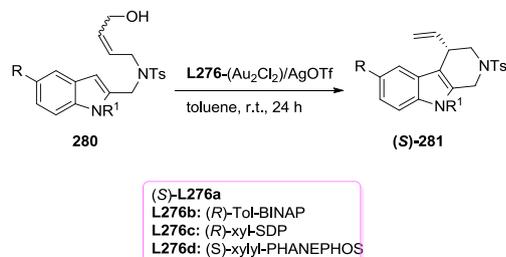
Scheme 89. Intramolecular asymmetric allylic alkylation of **280a-f**.

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

| Entry	L	R, R^1	Yield (%)	ee (%)
1	**L276b**	H, Me ((Z)-**280a**)	72 (**281a**)	40 (R)
2	**L276c**	H, Me ((Z)-**280a**)	50 (**281b**)	56
3	**L276d**	H, Me ((Z)-**280a**)	71 (**281c**)	80
4	(S)-**L276a**	H, Me ((Z)-**280a**)	75 (**281d**)	80
5	(S)-**L276a**	H, Me ((Z)-**280a**)	62 (**281e**)	68
6	(S)-**L276a**	Cl, Me ((Z)-**280b**)	93 (**281f**)	79
7	(S)-**L276a**	Me, Me ((Z)-**280c**)	75 (**281g**)	80
8	(S)-**L276a**	MeO, Me ((Z)-**280d**)	61 (**281h**)	76
9	(S)-**L276a**	H, Bn ((Z)-**280e**)	95 (**281i**)	70
10	(S)-**L276a**	H, allyl ((Z)-**280f**)	72 (**281j**)	78

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

Entry	Product	R	Yield (%)	ee (%)
1		R^1 = H	73 (**284a**)	56
2		R^1 = 6-Me	67 (**284b**)	63
3		R^1 = 6,7-(MeO)$_2$	57 (**284c**)	32
4		R^1 = 7-F	65 (**284d**)	89
5		R^2 = cyclopropyl	95 (**284e**)	54
6		R^2 = n-butyl	80 (**284f**)	10
7		R^3 = 7-Me	55 (**284g**)	43
8		R^3 = 5-MeO	26 (**284h**)	48
9		R^3 = 6-Cl	50 (**284i**)	33
10		–	41 (**284j**)	59

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].
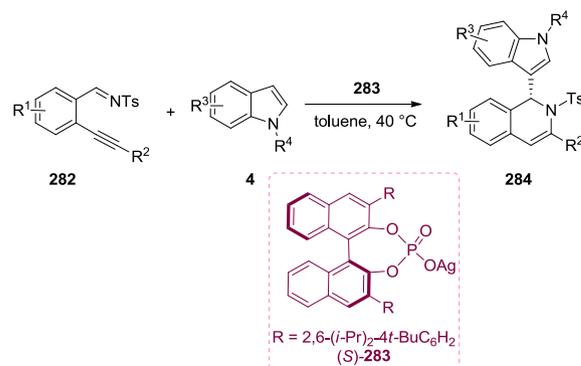
Scheme 90. Ag(I)-catalyzed enantioselective synthesis of 1,2-dihydroisoquinolines.
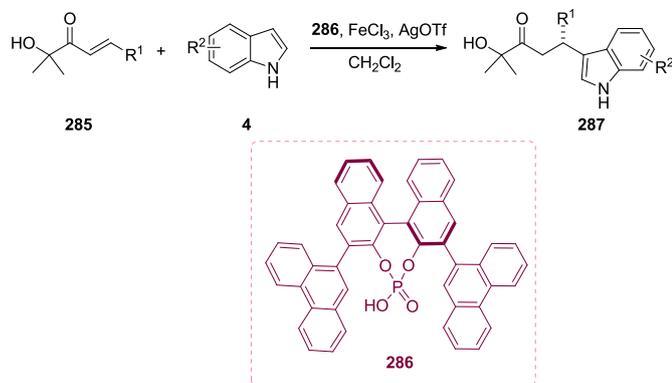
Scheme 91. F-CA of indoles with α'-hydroxy enones catalyzed by combined FeCl₃/Brønsted acid **286**/AgOTf.

Table 57
F-CA of indoles with α'-hydroxy enones catalyzed by combined FeCl₃/Brønsted acid **286**/AgOTf.

| Entry	R¹	R²	T (°C)	Yield (%)	ee (%)
1	4-ClPh	H	−40	83	90
2	4-MeOPh	H	−20	76	73
3	4-F₃CPh	H	−40	90	91
4	4-O₃NPh	H	−40	68	84
5	3-ClPh	H	−20	82	85
6	2-ClPh	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-ClPh	5-Br	−20	82	72
11	4-ClPh	2-Me	−20	86	24
12	4-ClPh	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 β-aryl α'-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 β-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 β,γ-unsaturated α-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 β,γ-unsaturated α-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, α-keto ester **239b** including an isopropyl ester substituent was an inactive substrate, and is maybe because
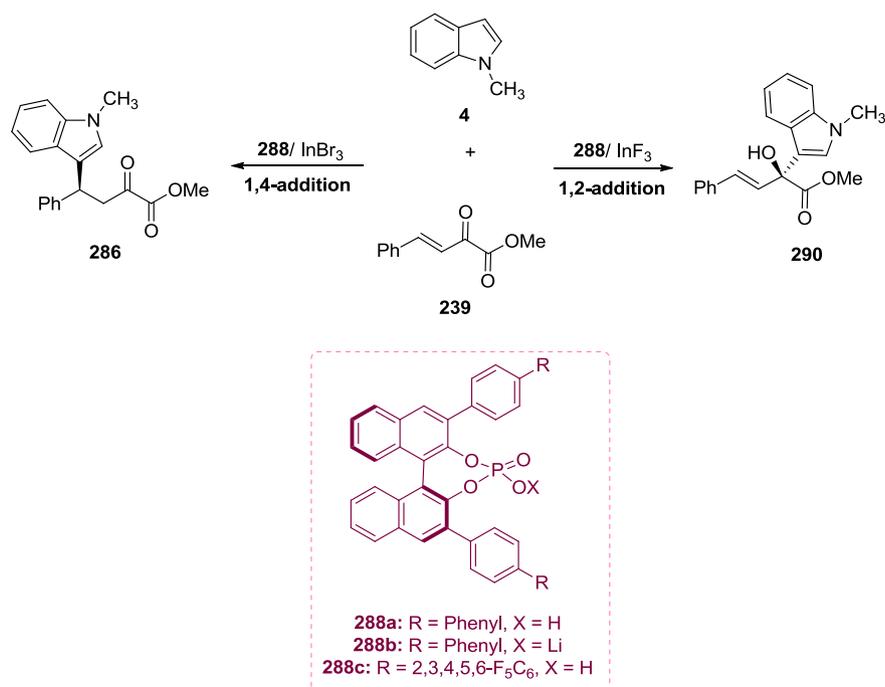
Scheme 92. Regioselective and enantioselective 1,2- and 1,4-addition.
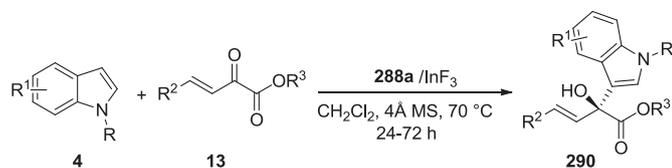
Scheme 93. Enantioselective 1,2-addition of *N*-protected indoles **4** and various α-keto esters **13**.
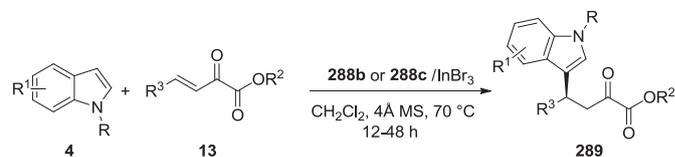
Scheme 94. Enantioselective 1,4-addition of *N*-protected indoles **4** and various α-ketoesters **13**.

Table 58

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

Entry	Product	Entry	Product
1	**290a** 82% yield, 93% *ee*	7	**290g** 63% yield, 99% *ee*
2	**290b** trace	8	**290h** 56% yield, 93% *ee*
3	**290c** 85% yield, 96% *ee*	9	**290i** 75% yield, 82% *ee*
4	**290d** 77% yield, 95% *ee*	10	**290j** 61% yield, 93% *ee*
5	**290e** 70% yield, 89% *ee*	11	**290k** 35% yield, 94% *ee*
6	**290f** 73% yield, 92% *ee*	12	**290l** trace

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 **4**. These transformations afforded the corresponding 1,4-addition adducts **289a-l** 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].
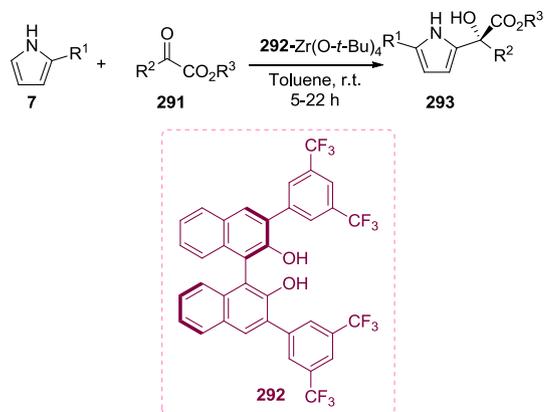
2.8. Zirconium

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 upon oxidation with *p*-benzoquinone [138]. Based on the optimal reaction conditions, the effect of the ester substituent in substrates **291** was examined the. The greatest outcomes in terms of enantioselectivity and yield have been provided by using ethyl and trichloroethyl ester derivatives, whereas several ester derivatives such as benzyl, methyl or isopropyl afforded the desired products with excellent enantioselectivity but lower yields. Thus, ethyl 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 consequences in terms of yields and *ee*s than those comprising strong electron-donating such as methoxy or electron-withdrawing such as −NO₂ or −CN 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	**289a** 288c: 98% yield, 97% *ee* 288b: 90% yield, 95% *ee*	7	**289g** 288c: 90% yield, 90% *ee*
2	**289b** 288c: trace 288b: 87% yield, 93% *ee*	8	**289h** 288c: 87% yield, 93% *ee* 288b: 75% yield, 70% *ee*
3	**289c** 288c: 97% yield, 99% *ee* 288b: 95% yield, 90% *ee*	9	**289i** 288c: 98% yield, 97% *ee*
4	**289d** 288c: 95% yield, 98% *ee* 288b: 92% yield, 97% *ee*	10	**289j** 288c: 75% yield, 95% *ee*
5	**289e** 288c: 85% yield, 88% *ee* 288b: 90% yield, 88% *ee*	11	**289k** 288c: 65% yield, 79% *ee* 288b: 70% yield, 93% *ee*
6	**289f** 288c: 91% yield, 98% *ee* 288b: 93% yield, 97% *ee*	12	**289k** 288c: 70% yield, 65% *ee* 288b: 65% yield, 79% *ee*

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 (**7a**)	Ph, Et (**291a**)	79 (**293aa**)	98
2	H (**7a**)	Ph, Me (**291b**)	55 (**293 ab**)	97
3	H (**7a**)	Ph, *i*Pr (**291c**)	58 (**293ac**)	98
4	H (**7a**)	Ph, *t*Bu (**291d**)	33 (**293ad**)	90
5	H (**7a**)	Ph, Bn (**291e**)	49 (**293ae**)	97
6	H (**7a**)	Ph, CH₂Cl₃ (**291f**)	79 (**293af**)	97
7	H (**7a**)	4-MeC₆H₄, Et (**291g**)	56 (**293 ag**)	97
8	H (**7a**)	2-MeC₆H₄, Et (**291h**)	13 (**293ah**)	65
9	H (**7a**)	4-MeOC₆H₄, Et (**291i**)	35 (**293ai**)	98
10	H (**7a**)	4-ClC₆H₄, Et (**291j**)	69 (**293aj**)	96
11	H (**7a**)	4-NCC₆H₄, Et (**291k**)	62 (**293ak**)	81
12	H (**7a**)	4-O₂NC₆H₄, Et (**291l**)	77 (**293 al**)	60
13	H (**7a**)	3,5-F₂C₆H₃, Et (**291m**)	72 (**293am**)	77
14	H (**7a**)	2-naphthyl, Et (**291n**)	63 (**293an**)	98
15	H (**7a**)	2-thiophenyl, Et (**291o**)	68 (**293ao**)	95
16	H (**7a**)	2-furanyl, Et (**291p**)	43 (**293ap**)	90
17	H (**7a**)	PhCH₂CH₂, Et (**291q**)	30 (**293aq**)	46
18	Et (**7b**)	Ph, Et (**291a**)	82 (**293ba**)	92
19	Et (**7b**)	4-MeC₆H₄, Et (**291g**)	62 (**293bg**)	93
20	Et (**7b**)	4-ClC₆H₄, Et (**291j**)	67 (**293bj**)	83
21	CH₃COCH₂CH₂ (**7c**)	Ph, Et (**291a**)	71 (**293ca**)	96

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 *ee*s. Lastly, ethyl (3,5- difluorophenyl)oxoacetate **291m**, containing two additional groups on the phenyl ring, afforded the desired alkylated pyrrole **293am** with a moderate yield and *ee*. Inappropriately, the reaction with the aliphatic α-ketoester **291q** 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 *ee*s 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 titanium^IV and a dimeric structure in the cases of zirconium(IV) and hafnium(IV). The dimeric structure with a doubly bridged scaffold [Zr(IV) ₂(μ-(*R*)-3,3′-Br₂-BINOL)₂] in which every binaphthol ligand serves as bridge between the metal centers (Novak's model) is more stable than the dimeric structure with a doubly bridged
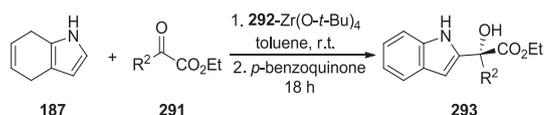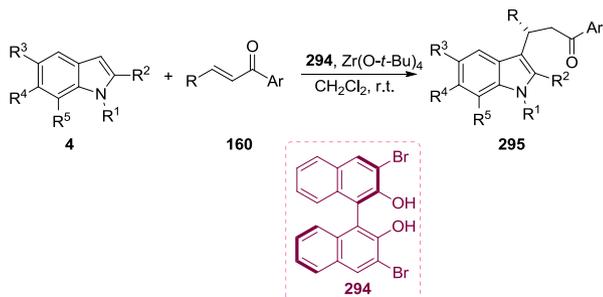

Scheme 96. AF-C reaction of 4,7-dihydroindole **187** and α-ketoesters **291** catalyzed by **292**-(O-*t*-Bu)₄.

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

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 (**291n**)	74 (**293n**)	90
5	2-thiophene-yl (**291o**)	51 (**293o**)	84

Scheme 97. AF-C reaction of indoles with α,β-unsaturated ketones Zr(O-*t*-Bu)₄-**294**.

Table 62
AF-C reaction of indoles with α,β-unsaturated ketones Zr(O-*t*-Bu)₄-**294**.

Entry	Ar, R	Yield (%)	*ee* (%)
1	Ph, Me	87 (**295aa**)	97
2	Ph, Et	87 (**295 ab**)	94
3	Ph, Pr	82 (**295ac**)	97
4	Ph, Ph	25 (**295ad**)	96
5	*p*-MeC₆H₄, Me	91 (**295ae**)	95
6	*m*-MeC₆H₄, Me	84 (**295af**)	92
7	*o*-MeC₆H₄, Me	73 (**295 ag**)	72
8	*p*-MeOC₆H₄, Me	54 (**295ah**)	95
9	*p*-FC₆H₄, Me	92 (**295ai**)	96
10	*p*-BrC₆H₄, Me	95 (**295aj**)	97
11	2-naphthyl, Me	89 (**295ak**)	98
12	2-thienyl, Me	87 (**295 al**)	96

scaffold [Zr(IV)₂(μ-OtBu)₂] in which the *tert*-butoxide substituents serve as bridging ligands (Kobayashi's model). The generality of the F-CA based on the indole structure was explored (Scheme 97, Table 62) [140].

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*s, 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*-F or *para*-F, products **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
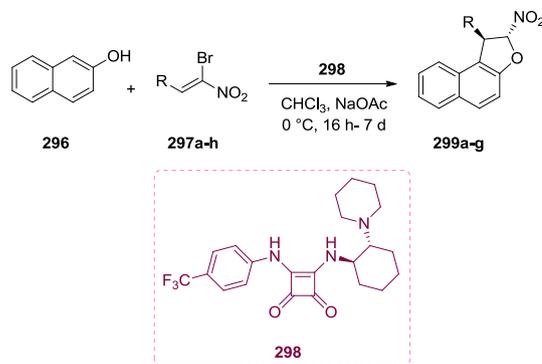
Scheme 98. AF-C reaction for the synthesis of *trans*-dihydronaphthofurans.

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

Entry	R	Yield (%)	*ee* (%)
1	Ph (**297a**)	71 (**299a**)	98
2	4-MeC₆H₄ (**297b**)	85 (**299b**)	94
3	4-MeOC₆H₄ (**297c**)	45 (**299c**)	94
4	2-FC₆H₄ (**297d**)	94 (**299d**)	88
5	4-FC₆H₄ (**297e**)	59 (**299e**)	97
6	4-BrC₆H₄ (**297f**)	78 (**299f**)	92
7	4-BrC₆H₄ (**297f**)	72 (**299f**)	92
8	*n*Bu (**297g**)	55 (**299g**)	91
9	*t*Bu (**297h**)	n.r.	−

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 enantiomeric excesses. The corresponding products provided are synthetic intermediates for the formation of tetrahydroprotoberberine alkaloids. This procedure was used in the first stereoselective synthesis of 13-methyl tetrahydroprotoberberine. 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*)-pyrrolidinylisoquinoline **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** produced **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 sulfonamide and triphosgene. To evaluate this catalyst, it was examined the AF-CA reaction of nitrostyrene and pyrrole [145]. Based on the optimal conditions described in Scheme
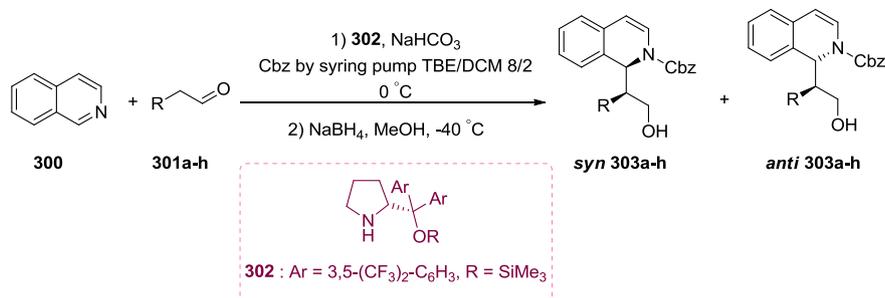
Scheme 99. Organocatalytic alkylation reaction of isoquinolines **300** with different aldehydes.

Table 64
Organocatalytic alkylation reaction of isoquinoline **300** with different aldehydes.

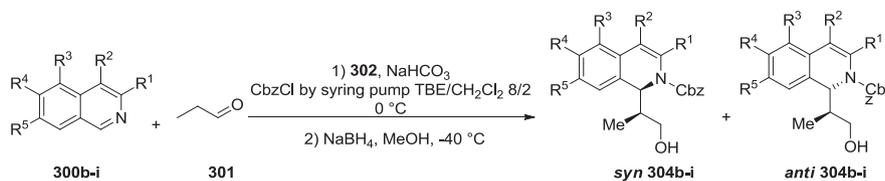| Entry	R	303	Yield	dr	ee (%) (syn)	ee (%) (anti)
1	Me (**301a**)	**303a**	53	74/26	96	87
2	Et (**301b**)	**303b**	5 (39/12)	77/23	98	98
3	H (**301c**)	**303c**	10	50	–	–
4	-(CH₂)₅Me (**301d**)	**303d**	65	79/21	99	96
5	-(CH₂)₃Cl (**301e**)	**303e**	13	73/27	97	80
6	-(CH₂)Ph (**301f**)	**303f**	9 (7/2)	81/19	91	93
7	cis-CH₂CH=CHCH₂Me (**301g**)	**303g**	23	32/68	81	94
8	Ph (**301h**)	**303h**	62	33/67	82	90

Scheme 100. Organocatalytic alkylation reaction of different isoquinolines with **301**.

**Table 65**
Organocatalytic alkylation reaction of different isoquinolines with **301**.

Entry	R¹, R², R³, R⁴, R⁵	Yield (%)	dr	ee (%) (syn)	ee (%) (anti)
1	H, H, Br, H, H (**300b**)	40 (**304b**)	73/27	95	88
2	Me, H, H, H, H (**300c**)	23 (**304c**)	87/13	99	94
3	H, H, H, MeO, MeO (**300d**)	54 (**304d**)	19/81	54	48
4	H, H, H, MeO, MeO (**300d**)	53 (**304d**)	29/71	−77	91
5	H, H, allyl, H, H (**300e**)	56 (**304e**)	76/44	96	86
6	H, H, H, MeO, H (**300f**)	56 (**304f**)	54/46	78	25
7	H, H, H, Me, H (**300g**)	68 (**304g**)	58/42	83	7
8	H, H, H, Me, H (**300g**)	75 (**304g**)	47/53	88	92
9	H, Bn, H, H, H (**300i**)	60 (**304i**)	81/19	97	74

101, it was provided the corresponding product with poor selectivity. A control reaction without catalyst displayed very little background reaction. They postulated that the lack of selectivity can be because of an unfavored conformation in which the chiral elements in the catalyst are away from the incipient chiral center Fig. 17. The oxygens on the sulfonyl and carbonyl substituents contain limited undesirable charges and the dipole-dipole repulsion between these substituents is anticipated to drive them away from each other. Remarkably, this would place the chiral camphor substituents away from the hydrogen bond donors. Once nitrostyrene links the urea **305** 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
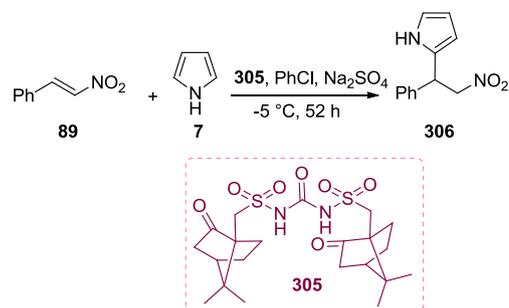
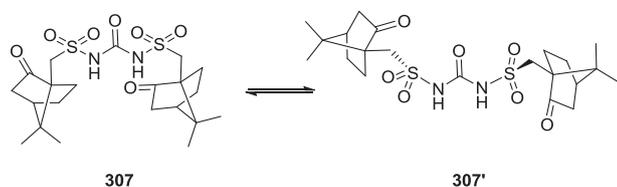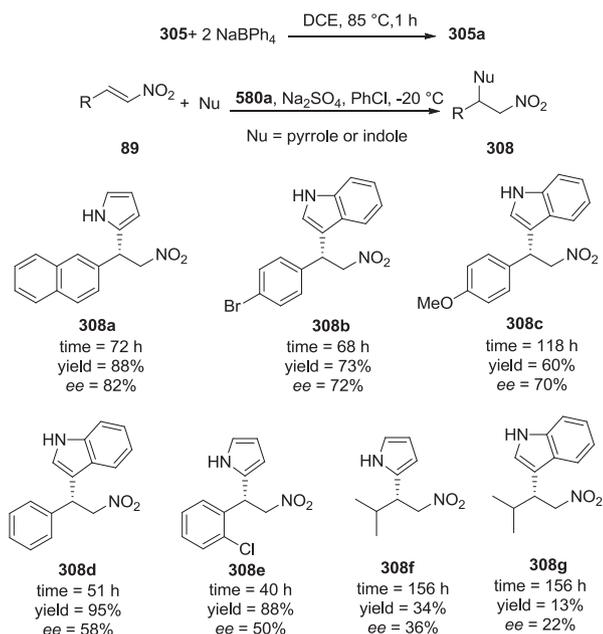**Scheme 101.** AF-C reaction mediated by **305**.

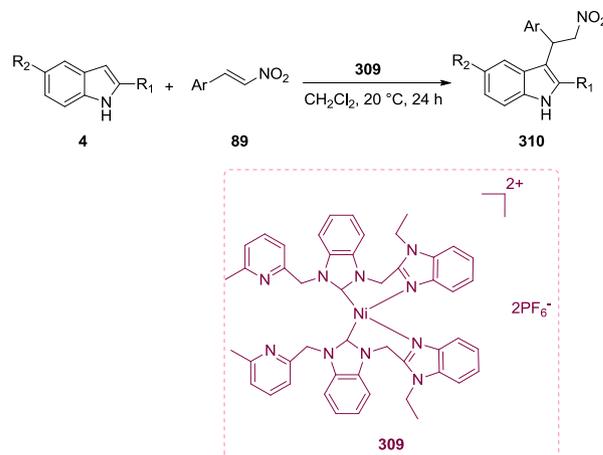**Fig. 17.** Proposed conformational equilibrium between **307**/**307'**.

Scheme 102. Scope of F–C reaction.

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

Table 66
F–C reaction of indoles with β-nitrostyrenes catalyzed by complex **309**.

Entry	R^1	R^2	Ar	Yield (%)
1	H	H	Ph	85 (**310a**)
2	H	H	2-MeOC$_6$H$_4$	76 (**310b**)
3	H	H	3-MeOC$_6$H$_4$	78 (**310c**)
4	H	H	4-MeOC$_6$H$_4$	80 (**310d**)
5	H	H	4-ClC$_6$H$_4$	77 (**310e**)
6	H	H	4-BrC$_6$H$_4$	53 (**310f**)
7	H	H	Furan	71 (**310g**)
8	H	H	4-O$_2$NC$_6$H$_4$	39 (**310h**)
9	Me	H	Ph	84 (**310i**)
10	Me	H	3-MeOC$_6$H$_4$	77 (**310j**)
11	Me	H	2-MeOC$_6$H$_4$	96 (**310k**)
12	Me	H	4-ClC$_6$H$_4$	95 (**310l**)
13	Me	H	4-MeOC$_6$H$_4$	77 (**310m**)
14	Me	H	Furan	87 (**310n**)
15	Me	H	4-BrC$_6$H$_4$	88 (**310o**)
16	Me	H	1-naphthyl	81 (**310p**)
17	H	MeO	C$_3$H$_5$	44 (**310q**)
18	H	MeO	Furan	53 (**310r**)

electron donating and withdrawing scaffolds served well in the current reaction whereas, nitroalkene derivatives containing alkyl groups reacted more slowly (Scheme 102) [145].

2.10. Nickel

[Ni(L2)$_2$(CH$_3$CN)](PF$_6$)$_2$ (**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 temperature 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 substituent at the 2-position, made the desired adducts in high yields. In the following, 5-(methoxy)-1H-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 NO$_2$ substituents provided a lesser yield, in opposition to, the β-nitrostyrene 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–CF$_3$–β-difunctionalized nitroalkene derivatives has been accomplished with

Ni(ClO$_4$)$_2$-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 **313la**, 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 C$_2$ F-CA reaction of *N*-methyl skatole and β,γ-unsaturated α-ketoester derivatives was achieved with a chiral *N*,*N'*-dioxide-Ni(II) system. Based on optimal conditions, the desired indoles have been provided in moderate yield and high *ees* [150]. Feng and co-workers examined the alkylation reaction of *N*-methyl skatole **4** and β,γ-unsaturated α-ketoester **239** by using chiral Lewis acid catalysts of ligand **318**. They doubtful that a dearomatization compound could
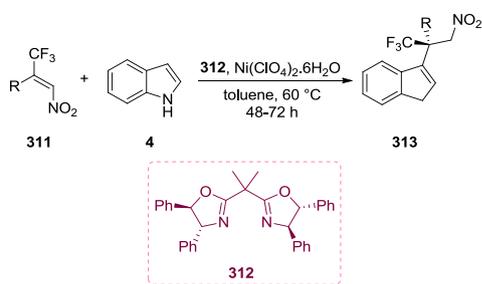
Scheme 104. AF-CA of indole derivatives and β–CF₃–β-difunctionalized nitroalkene derivatives with Ni(ClO₄)₂-bisoxazoline system.

Table 67
AF-CA of indole derivatives and β–CF₃–β-difunctionalized nitroalkene derivatives with Ni(ClO₄)₂-bisoxazoline system.

Entry	R	Yield (%)	ee (%)
1	Ph (**311a**)	95 (**313aa**)	96
2	Ph (**311a**)	88 (**313aa**)	96
3	3-MeC₆H₄ (**311b**)	87 (**313ba**)	95
4	4-MeC₆H₄ (**311c**)	91 (**313ca**)	96
5	2-MeC₆H₄ (**311d**)	n.d. (**313da**)	–
6	3-MeOC₆H₄ (**311e**)	82 (**313ea**)	92
7	4-MeOC₆H₄ (**311f**)	96 (**313fa**)	96
8	3,4-(MeO)₂C₆H₃ (**311g**)	78 (**313ga**)	88
9	3,5-(Me)₂C₆H₃ (**311h**)	72 (**313ha**)	93
10	4-ClC₆H₅ (**311i**)	72 (**313ia**)	82
11	3-FC₆H₅ (**311j**)	87 (**313ja**)	95
12	3- F₃CC₆H₅ (**311k**)	86 (**313ka**)	95
13	4-F₃CC₆H₅ (**311l**)	80 (**313la**)	95
14	3-thienyl (**311m**)	96 (**313ma**)	96
15	2-naphthyl (**311n**)	69 (**313na**)	95
16	Bn (**311o**)	78 (**313oa**)	33
17	2-Phenylethyl (**311p**)	88 (**313pa**)	97
18	3-Phenylpropyl (**311q**)	84 (**313qa**)	88
19	2-Phenoxybutyl (**311r**)	97 (**313ra**)	87
20	1-octyl (**311s**)	96 (**313sa**)	89

be provided from the initial C3 nucleophilic addition reaction of the *N*-methyl skatole to the β,γ-unsaturated α-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 β,γ-unsaturated α-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 *ee*s were provided, in spite of the electronic effect or the position of the groups on the aromatic ring of ketoester derivatives. Fused-ring functionalized β,γ-unsaturated

α-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 β,γ-unsaturated α-ketoester **239** links with nickel(II) created an intermediate. The *Si*-face of the β,γ-unsaturated α-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 α-functionalized β-nitroacrylates was achieved based on catalysis of Ni(ClO₄)₂-bisoxazoline system [153] at 1 mol % catalyst loading, giving chiral indolic β-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 *ee*s are usually high for α-aryl-β-nitroacrylate derivatives **322a-i** bearing both electron-donating substituents and electron-withdrawing substituents on the aromatic ring. However, no reaction happened for *o*-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 *ee*s (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 β,γ-unsaturated α-ketoester derivatives [156]. A vivid reversal of *ee* was recognized with ligands obtained from the similar kind of chiral source of L-ramipril, 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-RaPr₂–Ni(OTf)₂ system as the catalyst. Different β,γ-unsaturated α-ketoester derivatives having 2,5-dimethylpyrrole provided the desired products with high yields and *ee*s. Remarkably, the ester substituent had a small effect on the result. γ-Aryl
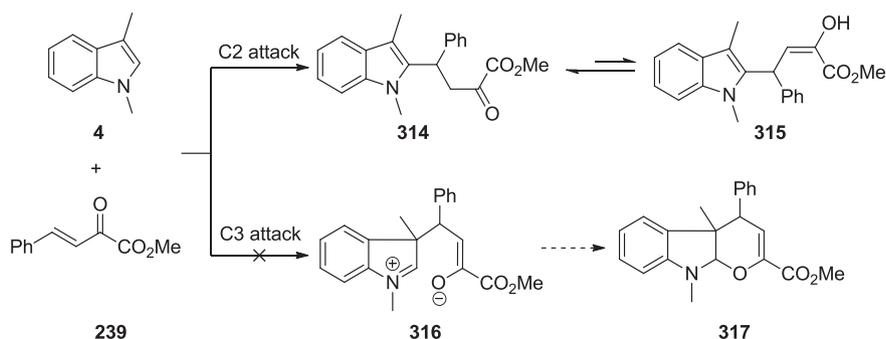
Scheme 105. F-CA of 3-substituted indoles and β,γ-unsaturated α-ketoesters.
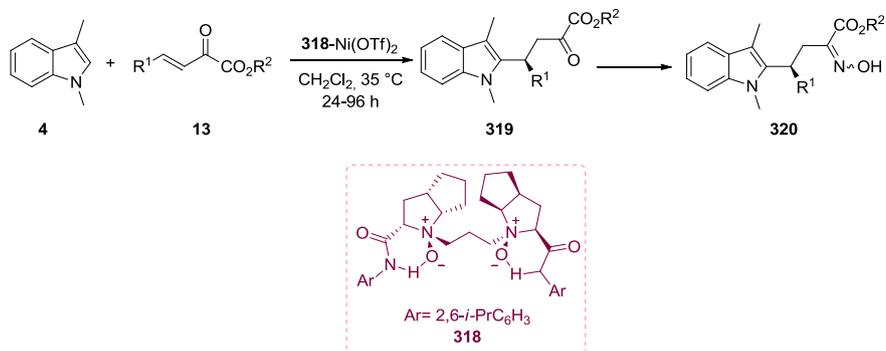
**Scheme 106.** Substrate scope of β,γ-unsaturated α-ketoesters in F-CA.

Table 68
Substrate scope of β,γ-unsaturated α-ketoesters in F-CA.

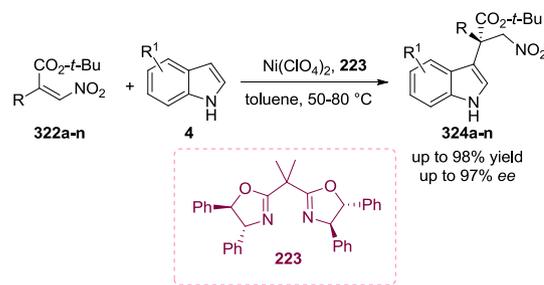| Entry	13, R^1, R^2	Yield of 319 (%)	*ee* of 320 (%)
1	Ph, Me	96	96
2	Ph, Et	90	95
3	Ph, *i*Pr	88	95
4	Ph, Bn	94	97
5	Ph, allyl	85	96
6	Ph, *t*Bu	95	99
7	2-FC$_6$H$_4$, Me	90	96
8	3-ClC$_6$H$_4$, Me	90	95
9	4-BrC$_6$H$_4$, Me	84	95
10	4-MeC$_6$H$_4$, Me	92	96
11	2-naphthyl, Me	74	96
12	2-thienyl, Me	88	96
13	3,4-Cl$_2$C$_6$H$_3$, Me	83	93
14	PhCH$=$CH$-$, Me	64	95
15	*c*-hexyl, Me	82	90

Table 69
AF-CA reaction of indole derivatives with acyclic α-functionalized β-nitroacrylates catalyzed by Ni(ClO$_4$)$_2$-bisoxazoline system.

Entry	R	Yield (%)	*ee* (%)
1	Ph (**322a**)	98 (**324a**)	96
2	3-MeC$_6$H$_4$ (**322b**)	98 (**324b**)	95
3	3-MeOC$_6$H$_4$ (**322c**)	98 (**324c**)	97
4	3-FC$_6$H$_4$ (**322d**)	97 (**324d**)	97
5	4-MeOC$_6$H$_4$ (**322e**)	97 (**324e**)	93
6	4-MeOC$_6$H$_4$ (**322e**)	63 (**324e**)	86
7	4-ClC$_6$H$_4$ (**322f**)	93 (**324f**)	93
8	4-F$_3$CC$_6$H$_4$ (**322g**)	98 (**324g**)	93
9	4-F$_3$CC$_6$H$_4$ (**322g**)	70 (**324g**)	87
10	3,4-MeO$_2$C$_6$H$_3$ (**322h**)	98 (**324h**)	95
11	3,5-Me$_2$C$_6$H$_3$ (**322i**)	98 (**324i**)	97
12	2-thienyl (**322j**)	97 (**324j**)	96
13	2-furyl (**322k**)	97 (**324k**)	95
14	2-naphthyl (**322l**)	98 (**324l**)	95
15	2-phenylethyl (**322m**)	89 (**324m**)	88
16	Bn (**322n**)	87 (**324n**)	88
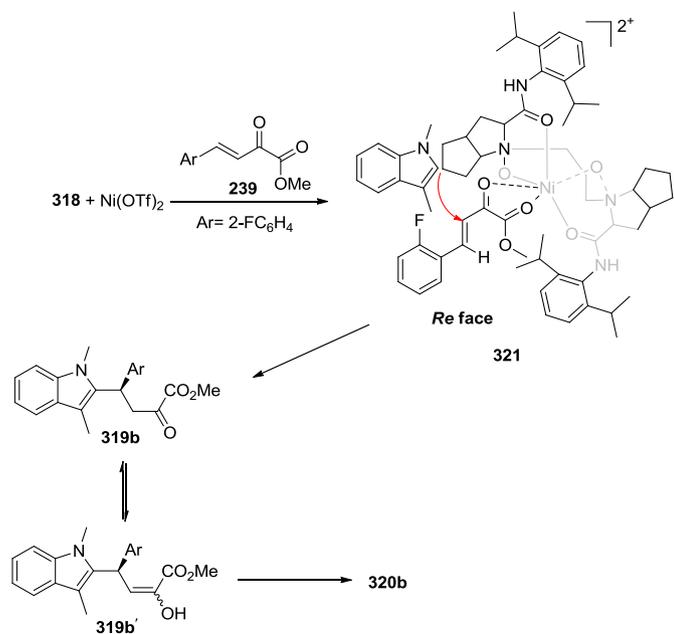
Scheme 107. The proposed catalytic model **321**.

Scheme 108. AF-CA reaction of indole derivatives with acyclic α-functionalized β-nitroacrylates catalyzed by Ni(ClO$_4$)$_2$-bisoxazoline system.

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 **326** by the application of the L-Ra*m*Bu$_2$-Ni(OTf)$_2$ system as the catalyst, instead. The F-CA reaction with 2,5-dimethylpyrrole was tolerable to different functionalized β,γ-unsaturated α-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,
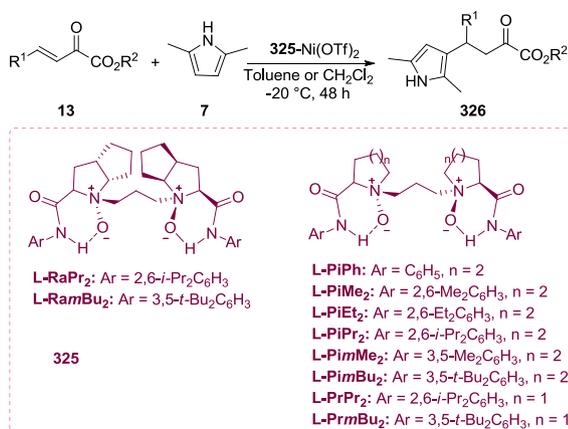
ketoester derivatives containing a halo-substituent at the ortho position undertook the reaction with relatively higher enantioselectivity than the others (up to 99% enantioselectivity). Electron-donating groups gave the corresponding products slowly in comparison with the electron-withdrawing substrates. Furthermore,

Scheme 109. Substrate scope of β,γ-unsaturated α-ketoesters **13**.

Scheme 110. Substrate scope of the AF-C reaction.

and (*E*)-phenylethenyl functionalized ones. Therefore, the two enantiomers of the 2,3,5-trifunctionalized pyrroles could be easily provided from chiral *N,N'*-dioxide derivatives with subtle change of the amide parts. Scale-up tests based on these conditions with 5 mmol of **13** gave both enantiomers in 90% yield, and 92% and 96% enantioselectivity. Lastly, the reaction of *N*-methyl 2,5-dimethyl pyrrole acted well, therefore giving the corresponding enantiomers in 76% chemical yield with 90% enantioselectivity, and 72% yield with 92% enantioselectivity. Remarkably, there was no contact between the catalyst and the NH of pyrrole (Scheme 109, Table 70) [156].

Using a nickel(II) perchlorate-bisoxazoline system as a catalyst, F-CA of 4,7-dihydroindole derivatives with β−CF$_3$−β-disubstituted nitroalkene derivatives have been explored with excellent *ee*s 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

Table 70
Substrate scope of β,γ-unsaturated α-ketoesters **13**.

| Entry	R^1	R^2	Yield (%)	ee (%)
1	Ph	Me	92 (95)	92 (95)
2	Ph	Et	84 (85)	95 (96)
3	Ph	Bn	91 (89)	92 (96)
4	Ph	*t*Bu	89 (89)	95 (93)
5	2-ClC$_6$H$_4$	Me	84 (91)	99 (67)
6	2-BrC$_6$H$_4$	Me	80 (78)	98 (60)
7	3-ClC$_6$H$_4$	Me	89 (93)	90 (90)
8	4-ClC$_6$H$_4$	Me	94 (95)	93 (93)
9	4-O$_2$NC$_6$H$_4$	Me	92 (89)	88 (92)
10	4-MeC$_6$H$_4$	Me	90 (93)	93 (93)
11	4-PhC$_6$H$_4$	Me	92 (91)	91 (94)
12	3-MeOC$_6$H$_4$	Me	82 (95)	93 (93)
13	4-MeOC$_6$H$_4$	Me	81 (78)	96 (94)
14	3,4-Cl$_2$C$_6$H$_3$	Me	90 (92)	91 (92)
15	1-naphthyl	Me	79 (80)	95 (91)
16	2-naphthyl	Me	89 (89)	93 (94)
17	2-thienyl	Me	84 (95)	92 (93)
18	2-furanyl	Me	94 (95)	92 (96)
19		Me	68 (95)	94 (91)
20		Me	85 (90)	91 (95)
21	*c*-hexyl	Me	78 (84)	86 (20)

Table 71
Substrate scope of the AF-C reaction.

Entry	R^1	R^2	Yield (%)	ee (%)
1	Ph (**311a**)	H (**187a**)	94 (**328aa**)	91
2	3-MePh (**311b**)	H (**187a**)	95 (**328ba**)	85
3	4-MePh (**311c**)	H (**187a**)	92 (**328ca**)	88
4	4-MeOPh (**311d**)	H (**187a**)	90 (**328da**)	88
5	3,5-Me$_2$Ph (**311e**)	H (**187a**)	90 (**328ea**)	84
6	4-ClPh (**311f**)	H (**187a**)	89 (**328fa**)	81
7	3-FPh (**311g**)	H (**187a**)	92 (**328ga**)	85
8	4-F$_3$CPh (**311h**)	H (**187a**)	88 (**328ha**)	86
9	3-thienyl (**311i**)	H (**187a**)	86 (**328ia**)	68
10	2-naphthyl (**311j**)	H (**187a**)	85 (**328ja**)	82
11	2-phenylethyl (**311k**)	H (**187a**)	84 (**328ka**)	71
12	1-octyl (**311l**)	H (**187a**)	88 (**328la**)	62
13	Ph (**311a**)	5-Me (**187b**)	90 (**328 ab**)	88
14	Ph (**311a**)	5-F (**187c**)	87 (**328ac**)	88
15	Ph (**311a**)	6-F (**187d**)	89 (**328ad**)	88

(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 *ee*s. Although, the reactivity was sharply effected by the steric influence of nitroalkene, 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 *ee*s 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 *ee*s in their reactions with nitroalkene **311a** (Scheme 110, Table 71) [157].

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 *ee*s. 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
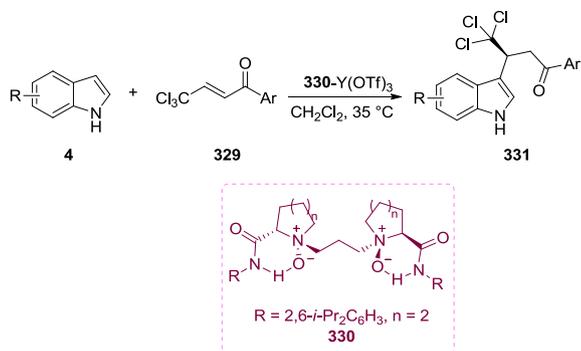
Scheme 111. Catalytic AF-CA of indoles **4** and β-trichloromethyl aryl enones **329**.
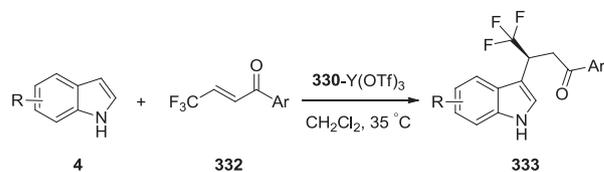
Table 72
Catalytic AF-CA of indoles **4** and β-trichloromethyl aryl enones **329**.

Entry	R	Ar	Yield (%)	ee (%)
1	H	Ph	89 (**331a**)	94 (*S*)
2	H	4-FC$_6$H$_4$	87 (**331b**)	91
3	H	4-ClC$_6$H$_4$	95 (**331c**)	92
4	H	4-BrC$_6$H$_4$	77 (**331d**)	88
5	H	4-O$_2$NC$_6$H$_4$	92 (**331e**)	95
6	H	4-MeC$_6$H$_4$	71 (**331f**)	90
7	H	3-ClC$_6$H$_4$	97 (**331g**)	92
8	H	3-O$_2$NC$_6$H$_4$	95 (**331h**)	93
9	H	2-ClC$_6$H$_4$	96 (**331i**)	91
10	H	2-FC$_6$H$_4$	96 (**331j**)	96
11	H	3,4-Cl$_2$C$_6$H$_3$	99 (**331k**)	90
12	H	2-naphthyl	95 (**331l**)	94
13	H	1-naphthyl	65 (**331m**)	91
14	H	2-thienyl	84 (**331n**)	85
15	5-Me	Ph	94 (**331o**)	90
16	6-Me	Ph	95 (**331p**)	90
17	7-Me	Ph	94 (**331q**)	86
18	5-MeO	Ph	99 (**331r**)	93
19	7-Et	Ph	98 (**331s**)	83
20	6-MeO	Ph	78 (**331t**)	90
21	5-Cl	Ph	68 (**331u**)	72
22	5-F	Ph	40 (**331v**)	82
23	H	Ph	85 (**331a**)	93 (*S*)

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 *ee*s (Scheme 111, Table 72).

Frequently, the β-trifluoromethyl aryl enone derivatives **332** displayed higher activity than β-trichloromethyl aryl enone derivatives **326**. Apparently, the CF$_3$ 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 *ee*s. 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-diisopropylphenyl substituent of *N,N'*-dioxide **330**, that leads to

Scheme 112. Catalytic AF-CA of indoles **4** and β-trifluoromethyl aryl enones **332**.

Table 73
Catalytic AF-CA of indoles **4** and β-trifluoromethyl aryl enones **332**.

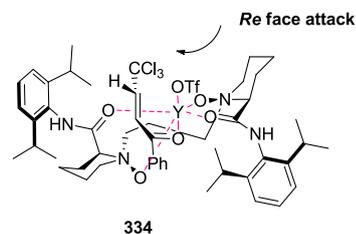| Entry	R	Ar	Yield (%)	ee (%)
1	H	Ph	96 (**333a**)	94 (*S*)
2	H	4-O$_2$NC$_6$H$_4$	99 (**333b**)	96
3	H	4-MeC$_6$H$_4$	95 (**333c**)	93
4	H	3-O$_2$NC$_6$H$_4$	99 (**333d**)	96
5	H	2-FC$_6$H$_4$	96 (**333e**)	92
6	H	4-ClC$_6$H$_4$	96 (**333f**)	80
7	H	2-naphthyl	88 (**333g**)	86
8	5-Me	Ph	99 (**333h**)	81
9	6-Me	Ph	87 (**333i**)	90
10	5-MeO	Ph	99 (**333j**)	96
11	6-MeO	Ph	99 (**333k**)	96
12	5-F	Ph	60 (**333l**)	79
13	H	Ph	99 (**333a**)	94 (*S*)

Fig. 18. Proposed model **334**.

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 *ee*s [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 (R^1 = Me and Bn). In contradiction of the electron-donating substituents that show a useful influence (R^2 = methoxy and methyl), the electron-withdrawing substituents (R^2 = Cl, F, Br, CN, CO$_2$Me) 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(imidazolinyl)phenyl (Phebim) ligand were described in 2012 by Song and co-workers [163]. One of the desired cationic chiral NCN pincer
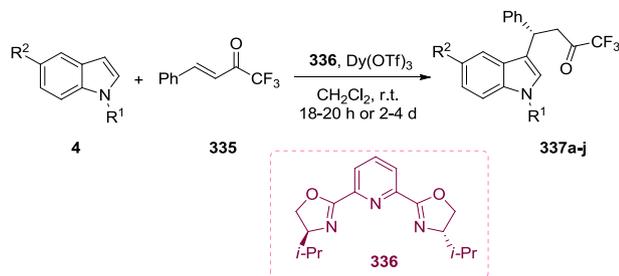
Scheme 113. Enantioselective AF-CA of indoles and α,β-unsaturated trifluoromethyl ketone derivatives.

Table 74
Enantioselective AF-CA of indoles and α,β-unsaturated trifluoromethyl ketone derivatives.

Entry	R^1	R^2	Yield (%)	ee (%)
1	H	H	95 (337a)	84
2	Me	H	98 (337b)	16
3	Bn	H	77 (337c)	16
4	H	MeO	96 (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)	77
9	H	$MeCO_2$	97 (337i)	19
10	H	NC	60 (337j)	7

platinum (II) systems **338**, that includes H_2O 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*s (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 alkylation 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 alkylation was extended to indole or indole derivatives with different aromatic nitroalkene derivatives. Generally, the reactions of indole (65–83% *ee*) with nitroalkene derivatives afforded *ee*s 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 *ee*s, it looked to be hard to establish a clear fashion. For
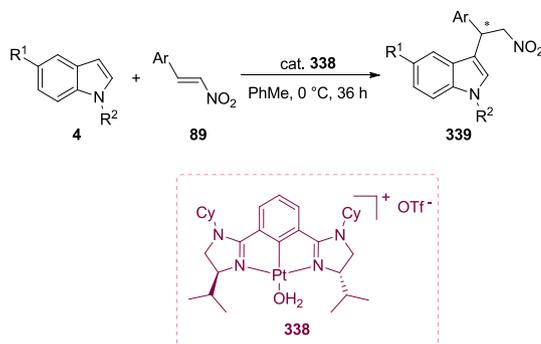
Scheme 114. AF-CA of indoles and nitroalkenes mediated by cationic pincer platinum (II) aquo complex **338**.

Table 75
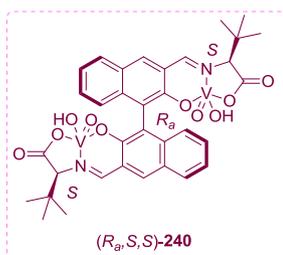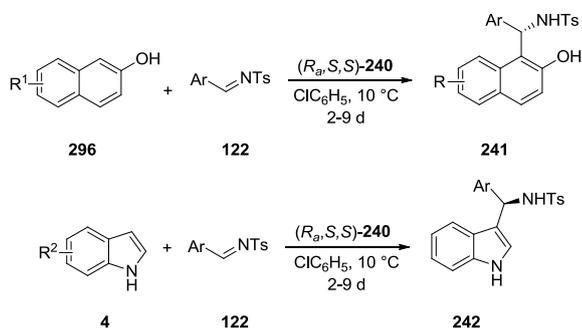AF-CA of indoles and nitroalkenes mediated by cationic pincer platinum (II) aquo complex **338**.

Entry	R^1, R^2	Ar	Yield (%)	ee (%)
1	H, H	Ph	99	69 (S)
2	H, H	Ph	84	78 (S)
3	H, H	Ph	43	81 (S)
4	H, H	p-FC_6H_4	73	65
5	H, H	p-ClC_6H_4	86	67
6	H, H	p-BrC_6H_4	60	71
7	H, H	p-$MeOC_6H_4$	81	83
8	H, H	p-$MeOC_6H_4$	93	65
9	Br, H	Ph	89	58
10	Br, H	Ph	77	70
11	Br, H	p-FC_6H_4	70	73
12	Br, H	p-ClC_6H_4	61	57
13	Br, H	p-BrC_6H_4	69	62
14	Br, H	p-$MeOC_6H_4$	61	57
15	MeO, H	Ph	72	34
16	MeO, H	p-FC_6H_4	58	36
17	MeO, H	p-ClC_6H_4	79	39
18	MeO, H	p-BrC_6H_4	70	46
19	MeO, H	p-$MeOC_6H_4$	65	64
20	H, Me	p-$MeOC_6H_4$	trace	–

instance, in the case of indole or 5-methoxyindole, the nitroalkene that had a *para*-$CH_3OC_6H_4$ scaffold gave the highest *ee*s compared with those including a Ph, p-F, p-Cl, or p-BrC_6H_4 scaffold based on same conditions, whereas in the case of 5-bromoindole, the nitroalkene bearing a p-FC_6H_4 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 homocoupling 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_a,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_a,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 *ee*s. In 2013 Sasai and co-workers reported V

Scheme 115. Vanadium-mediated AF-C-type reactions of imines and 2-naphthols or indoles.

Fig. 19. Plausible transition state for the hetero-coupling reaction of imine and 2-naphthol.

Table 76
Dinuclear vanadium system (R_a,S,S)-**240** mediated AF-C-type reactions.

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-EtC$_6$H$_4$ (**122d**)	67 (**241d**)	81
5	H (**296a**)	4-MeOC$_6$H$_4$ (**122e**)	70 (**241e**)	71
6	H (**296a**)	3-ClC$_6$H$_4$ (**122f**)	70 (**241f**)	89
7	H (**296a**)	2-ClC$_6$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$_4$ (**122j**)	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 [(*R*)-**245**-Hf (O*t*Bu)$_4$].

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 [Hf{(*R*)-3,3′-Br$_2$—BIN(O*t*Bu)$_2$]$_2$ system were established to functionalize the C-3 position of the indole core with a side chain containing a 1,4-difunctionalized scaffold and a benzylic 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

mediated AF-C-type reactions of *N*-tosyl imine derivatives and 2-naphthols or indole derivatives. The dinuclear V system (R_a,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_a,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_a,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].
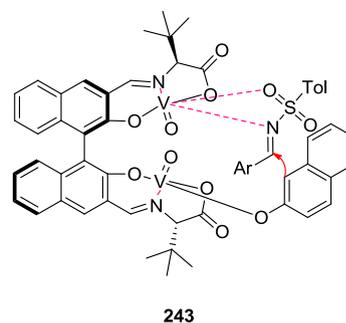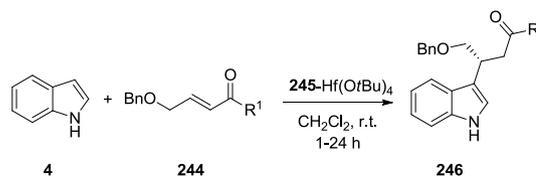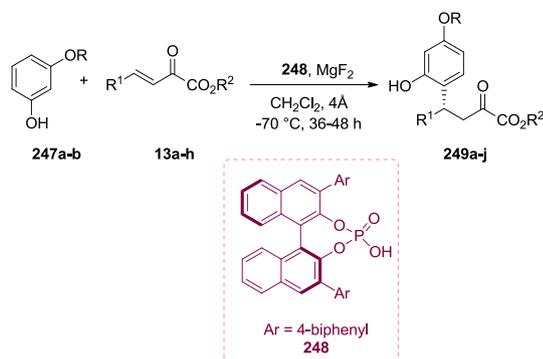
Table 77

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

Entry	R¹	Yield (%)	ee (%)
1	Ph (**244a**)	90 (**246aa**)	94
2	4-MeC₆H₄ (**244b**)	86 (**246ab**)	92
3	3-MeC₆H₄ (**244c**)	98 (**246ac**)	97
4	2-MeC₆H₄ (**244d**)	81 (**246ad**)	84
5	4-MeOC₆H₄ (**244e**)	45 (**246ae**)	87
6	4-BrC₆H₄ (**244f**)	78 (**246af**)	86
7	2-thienyl (**244g**)	90 (**246ag**)	92
8	2-furyl (**244h**)	93 (**246ah**)	84

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

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

Table 79

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

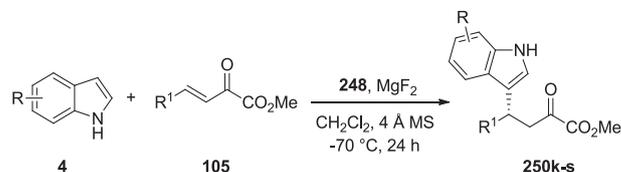| Entry	R	R¹	Yield (%)	ee (%)
1	H	Ph	82 (**250k**)	90 (R)
2	H	2-FC₆H₄	87 (**250l**)	94
3	H	4-ClC₆H₄	82 (**250m**)	83
4	H	3,4-Cl₂C₆H₃	80 (**250n**)	88
5	H	4-MeC₆H₄	78 (**250o**)	87
6	H	4-PhC₆H₄	81 (**250p**)	82
7	5-OMe	Ph	90 (**250q**)	92
8	5-OMe	Ph	81 (**250r**)	84
9	6-Cl	Ph	83 (**250s**)	92
10	6-Cl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

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 **5** 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 78

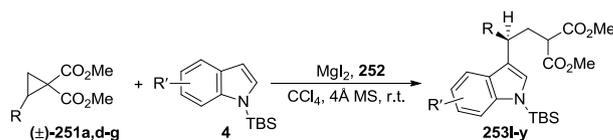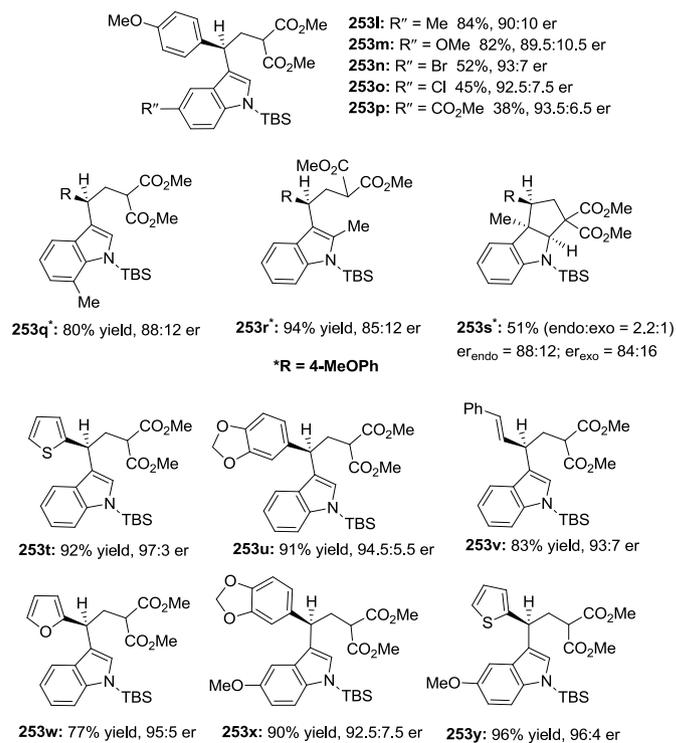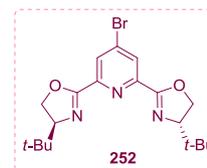F-CA reactions of **247a,b** and β,γ-unsaturated α-ketoesters **13**.

Entry	R	R¹	R²	Yield (%)	ee (%)
1	Me	Ph	Me	79 (**249a**)	95
2	Et	Ph	Me	80 (**249b**)	90
3	Me	4-ClC₆H₄	Me	70 (**249c**)	96
4	Et	4-ClC₆H₄	Me	65 (**249d**)	95
5	Me	3,4-Cl₂C₆H₃	Me	81 (**249e**)	>99
6	Me	3,4-Cl₂C₆H₃	Et	76 (**249f**)	86
7	Me	2-FC₆H₄	Me	82 (**249g**)	97
8	Me	4-MeC₆H₄	Me	57 (**249h**)	82
9	Me	3-MeC₆H₄	Me	75 (**249i**)	84
10	Me	4-PhC₆H₄	Me	59 (**249j**)	79

Scheme 119. An AF-CA of indole derivatives and donor-acceptor cyclopropanes.
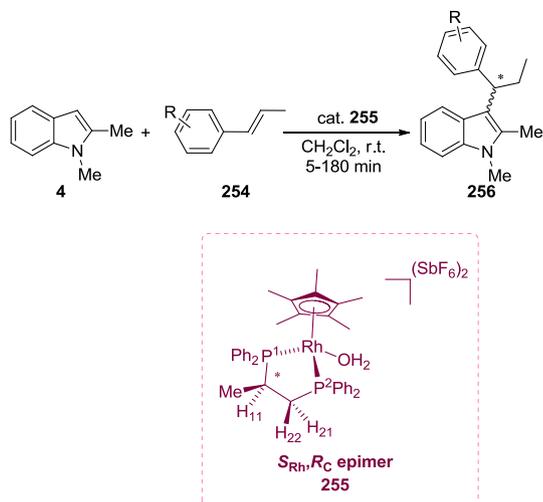
Scheme 120. AF-C reaction of *N*-Methyl-2-methylindole with *trans*-β-Nitrostyrenes.

Table 80
AF-C reaction of *N*-Methyl-2-methylindole with *trans*-β-Nitrostyrenes.

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

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)-[(η^5-C$_5$Me$_5$)Rh((R)-Prophos)(H$_2$O)][SbF$_6$]$_2$ (Prophos = propane-1,2-diylbis(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].

Based on the experimental data, the catalytic cycle presented in Scheme 121 can be suggested. The linked H$_2$O molecule in **255** was shown using *trans*-β-nitrostyrene, providing the nitroalkene system **257**. Indole attack on the stimulated C$_\beta$ 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 121. Proposed catalytic cycle for the AF-CA using **255**.
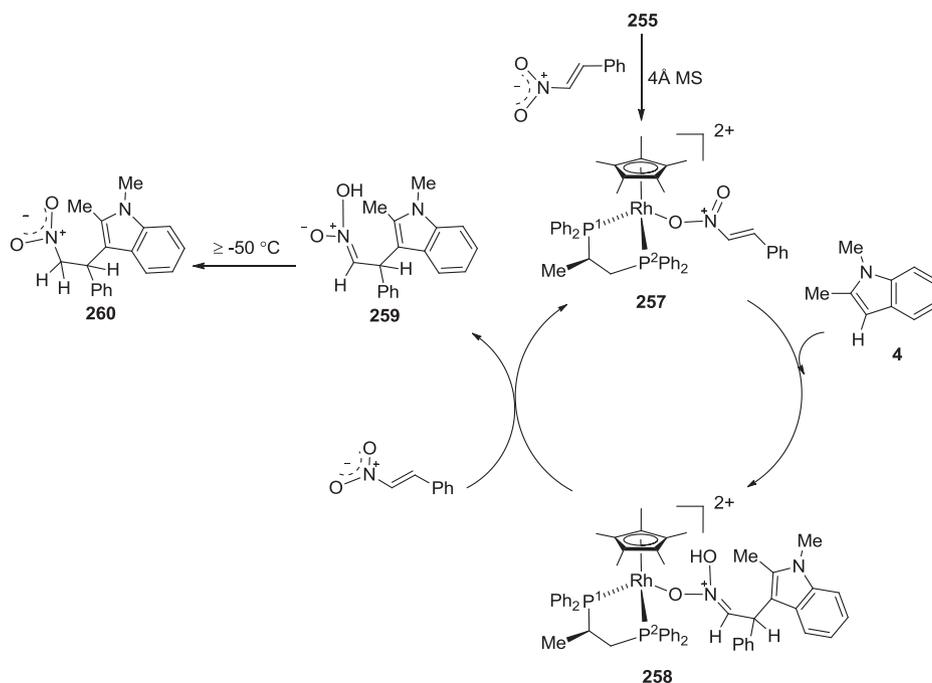
Table 81
AF-CA using **262**.

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
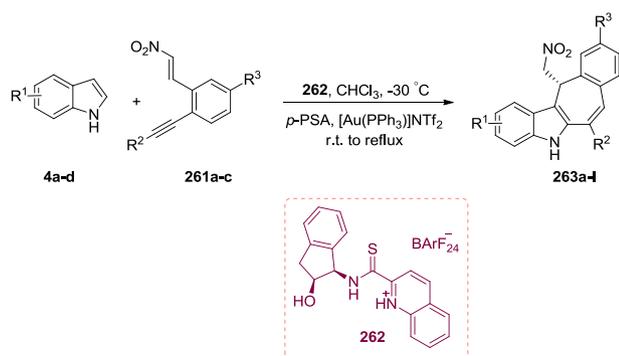
**Scheme 122.** AF-CA using **262**.

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 profounder 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 **4**, as well as 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, multi-catalytic 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**) (Scheme 122) [176].

Relied on the experiential data, as well as formerly reported investigations [177], a mechanism is suggested to clarify this multicatalytic 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 π-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
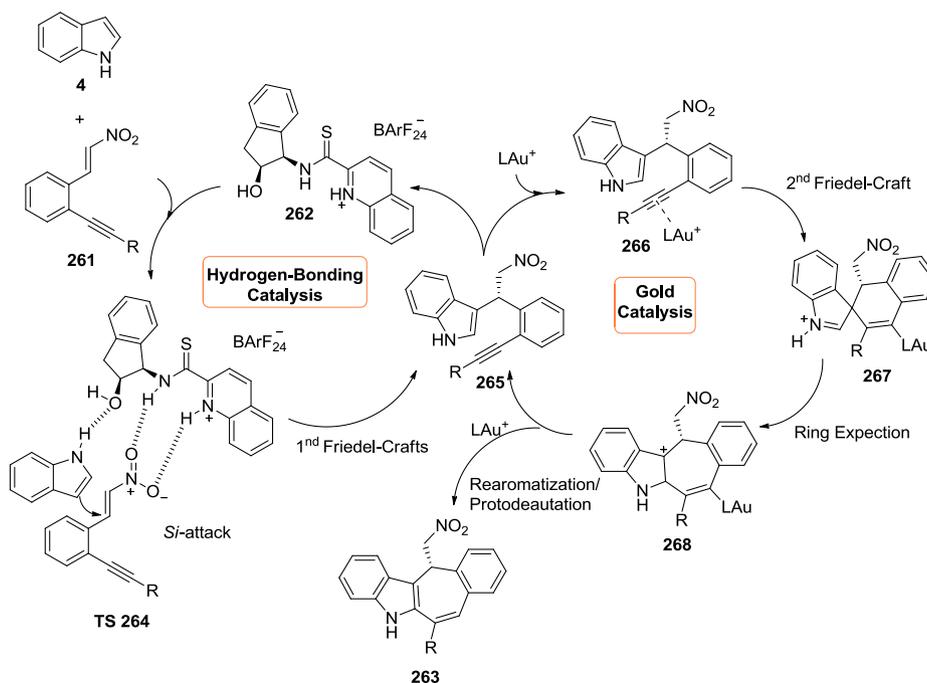
Scheme 123. Suggested mechanism of the sequential organo- and Au-based catalysis.
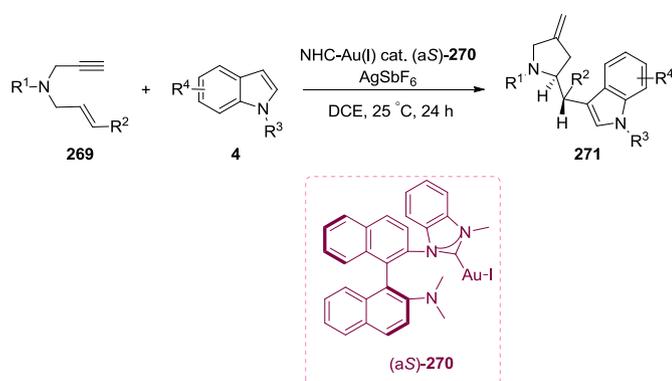
Scheme 124. The scope of the axially chiral Au system mediated enantioselective F–C/cyclization reaction of 1,6-enynes **269** and indoles **4**.

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 R^1 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 R^2 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 R^2 substituent did not contain an important influence on the reaction result. Besides, the R^3 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 R^2 was a hydrogen atom or an aliphatic substituent such as substrates **269j** ($R^2 = H$), **269k** ($2*R^2 = Me$), or **269l** ($2*R^2 = Me$), 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 *ee*s 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 *ee*s were obtained. However, the detected catalyst complex is appropriate for numerous substrates for both functionalized pyrroles and nitro-alkene derivatives (Scheme 125, Table 83) [181].

In 2012, Rueping et al. reported the initial enantioselective Ca-mediated addition of indoles to trifluoropyruvate derivatives. The relevant products were provided in excellent yields and with satisfactory to high *ee*s [182]. Based on the optimized reaction conditions, the generality of the enantioselective $Ca_3(PO_4)_2$-mediated F-CA reaction was examined (Table 84). The current reaction was performed using 1-naphthyl-substituted[H_8]-binol

Table 82
The scope of the axially chiral Au system mediated enantioselective F–C/cyclization reaction of 1,6-enynes **269** and indoles **4**.

Entry	R^1	R^2	R^3/R^4	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	*iPr*-substituted benzenesulfonyl	Ph (**269d**)	1-Me, H (**4a**)	67 (**271d**)	99:1	(+)2
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-ClC$_6$H$_4$ (**269g**)	1-Me, H (**4a**)	83 (**271g**)	99:1	(+)62
7	Ts	4-MeC$_6$H$_4$ (**269h**)	1-Me, H (**4a**)	87 (**271h**)	99:1	(+)60
8	Ts	4-MeOC$_6$H$_4$ (**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**)	1-Bn, 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**)	1-Bn, H (**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–N enyne (**269k**)	(**269k**)	1-Me, H (**4a**)	Complex	–	–
16	Ts–N enyne (**269l**)	(**269l**)	1-Me, H (**4a**)	Complex	–	–
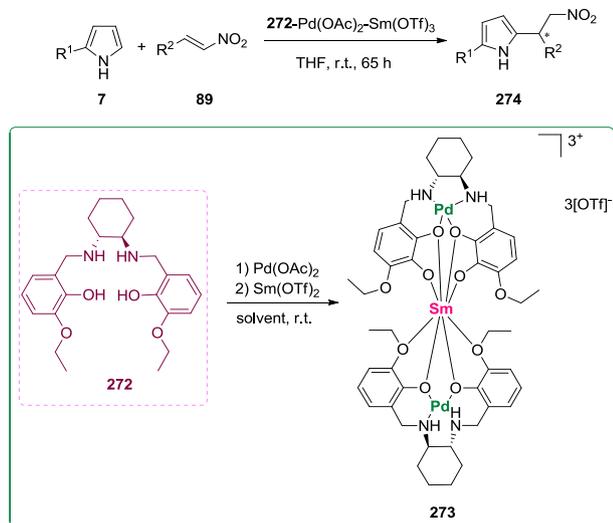
Scheme 125. Catalytic AF-C reaction of various pyrroles and nitroalkenes.

Table 83
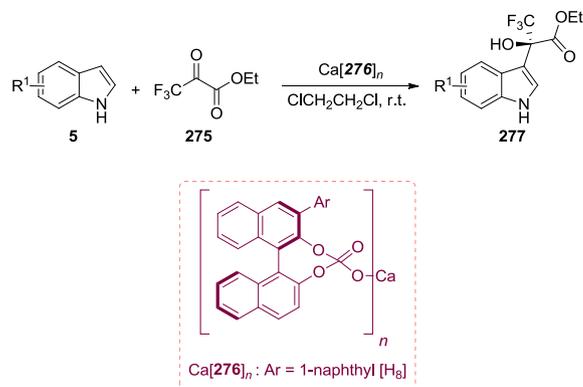Catalytic AF-C reaction of various pyrroles and nitroalkenes.

Entry	R^1	R^2	Yield (%)	ee (%)
1	H (**7a**)	Ph (**89a**)	86 (**274a**)	85
2	H (**7a**)	4-FC$_6$H$_4$ (**89b**)	92 (**274b**)	91
3	H (**7a**)	4-ClC$_6$H$_4$ (**189c**)	94 (**274c**)	71
4	H (**7a**)	4-BrC$_6$H$_4$ (**89d**)	93 (**274d**)	80
5	H (**7a**)	4-MeOC$_6$H$_4$ (**89e**)	92 (**274e**)	89
6	H (**7a**)	2-furyl (**89f**)	95 (**274f**)	85
7	H (**7a**)	2-thiophenyl (**89g**)	86 (**274g**)	93
8	H (**7a**)	nBu (**89h**)	55 (**274h**)	59
9	Et (**7b**)	Ph (**89a**)	86 (**274i**)	66
10	Et (**7b**)	4-BrC$_6$H$_4$ (**89d**)	90 (**274j**)	50
11	Et (**7b**)	2-furyl (**89f**)	92 (**274k**)	85
12	Et (**7b**)	2-thiophenyl (**89g**)	94 (**274l**)	87

Table 84
Scope of the AF-CA

Entry	R^1	Yield (%)	ee (%)
1	H	92 (**277a**)	83
2	5-F	94 (**277b**)	84
3	5-Cl	93 (**277c**)	84
4	5-Br	98 (**277d**)	85
5	5-I	98 (**277e**)	79
6	5-NC	90 (**277f**)	87
7	6-F	96 (**277g**)	89
8	6-Cl	98 (**277h**)	87
9	5-Me	99 (**277i**)	82
10	5-MeO	98 (**277j**)	82
11	7-Me	99 (**277k**)	87
12	7-Et	98 (**277l**)	84

Scheme 126. Scope of the AF-CA.

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 stereocontrol. 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 imperious attempts toward metal-catalyzed AF-CA were collected, herein.

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calcium phosphate Ca[**276**]$_n$ 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 ees up to 89%. This approach permits access to biologically relevant fluorine-containing 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].

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