



Recent developments in enantioselective iron-catalyzed transformations

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1. Introduction

Metal-catalyzed organic reactions represent powerful tools in organic synthesis [1], especially asymmetric transition-metal catalysis allows many types of highly enantioselective transformations to be achieved. For a long time, these reactions have involved the use of metals, such as palladium, rhodium, copper, iridium and ruthenium. However, by the very fact of the higher abundance and lower costs and toxicity of iron catalysts in comparison with other transition metals, more ecologic and economic iron-catalyzed transformations represent a wide potential for future organic synthesis. Especially in the field of asymmetric iron-catalyzed reactions, an impressive amount of novel and various methodologies have been recently developed, allowing the synthesis of many chiral cyclic as well as acyclic products to be achieved with excellent enantioselectivities. For example, highly efficient enantioselective iron-mediated reductions of carbonyl compounds and derivatives, epoxidations, additions to alkenes, nucleophilic additions to carbonyl compounds and derivatives, sulfa-Michael additions, cross-coupling reactions, cyclizations, ring-opening of epoxides, domino reactions and miscellaneous reactions have been described in the last few years. The goal of this review is to collect the recent developments in all types of enantioselective iron-catalyzed transformations published since the beginning of 2015, since this field was most recently reviewed this year by Bauer and Knölker [2]. Previous to 2015, this field including more general racemic iron-catalyzed reactions was reviewed by various authors [3]. It must be noted that asymmetric iron-catalyzed reactions performed in the presence of special ligands, such as chiral N_2P_2 ligands [4] or bisoxazolines [5], were respectively the purposes of an account and a mini-review reported in 2016, albeit including only few recent references (\leq three references dating from 2015 and zero reference from 2016). Furthermore, in the same year, Fürstner reported a critical outlook on general iron catalysis but including only two references dating from 2015 to 2016 concerning asymmetric catalysis [6]. On the other hand, the field of racemic iron-catalyzed C–H bond activation has been the subject of different reports [7]. Moreover in 2016, Costas et al. published a focus review entitled “biologically inspired C–H and C=C oxidations with H_2O_2 catalyzed by iron coordination complexes” including only one reference dealing with asymmetric reactions dating from 2016 [8]. Earlier in 2014, the special field of iron cyclopentadienone complexes was the subject of a mini-review reported by Quintard and Rodriguez [9]. The present review is divided into ten sections according to the types of reactions, dealing successively with iron-catalyzed asymmetric reductions of carbonyl compounds and derivatives, epoxidations, additions to alkenes, nucleophilic additions to carbonyl compounds and derivatives, sulfa-Michael additions, cross-coupling reactions, cyclizations, ring-opening of epoxides, domino reactions and miscellaneous transformations.

2. Enantioselective reductions of ketones and imines

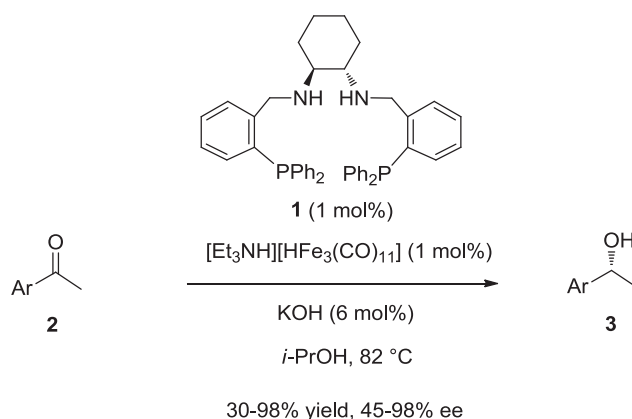
2.1. Asymmetric transfer hydrogenations of ketones and imines

The catalytic asymmetric reduction of carbonyl compounds is the most direct approach to chiral alcohols which represent pivotal intermediates in organic synthesis [10]. In most cases, catalysts

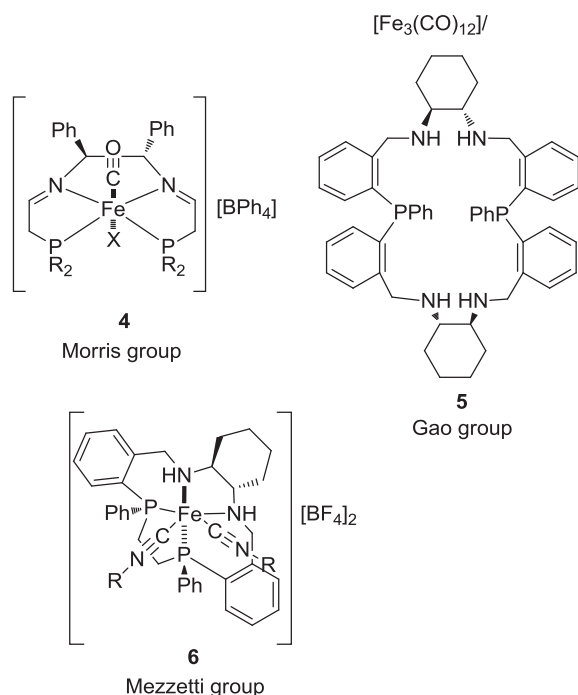
based on noble metals, such as ruthenium, rhodium and iridium, have been used to promote these reactions. However, replacing these expensive and toxic elements with more abundant and environmentally compatible transition metals, such as iron, is highly attractive. In this context, asymmetric iron-catalyzed transfer hydrogenations of ketones (and imines) have attracted increasing attention [11]. Actually, this field was pioneered by Gao et al. in 2004, who employed carbonyl iron complexes derived from chiral diaminodiphosphine P_2N_2 ligands, such as **1**, for the asymmetric transfer hydrogenation of aromatic ketones **2** in the presence of isopropanol as the hydrogen source [12]. The corresponding chiral alcohols **3** were obtained in moderate to good enantioselectivities excepted for the reduction of two sterically hindered ketones which provided excellent enantioselectivities (98% ee), as shown in Scheme 1.

Later, different groups, including those of Morris [13] and Mezzetti [14], independently investigated other chiral iron catalysts in enantioselective transfer hydrogenation of ketones (Scheme 2). For example, Morris et al. performed these reactions in the presence of more flexible diiminodiphosphine iron complexes, such as **4**, allowing enantioselectivities of up to 99% ee to be achieved by introducing bulky alkyl phosphines on the ligand moiety (Scheme 2) [15]. Comparable enantioselectivities were also described by Gao et al. by using a chiral iron catalyst generated from hexadentate P_2N_4 ligand **5** and $[Fe_3(CO)_{12}]$ (Scheme 2) [16]. In addition, Mezzetti et al. reported the synthesis of iron bis(isonitrile) complexes **6** bearing a C_2 -symmetric $(NH)_2P_2$ macrocycle, allowing enantioselectivities of up to 95% ee to be achieved (Scheme 2) [14].

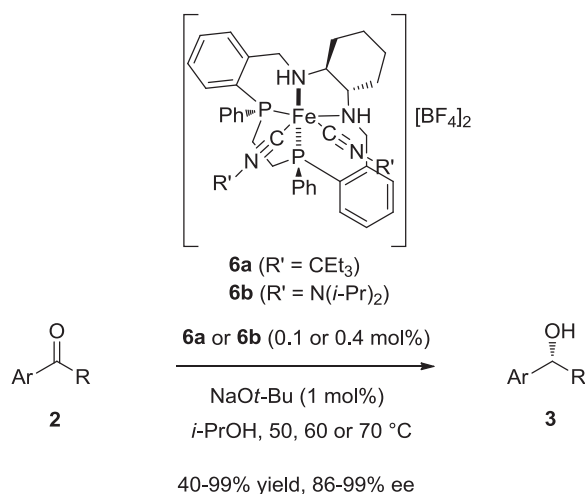
In 2015, Mezzetti et al. reported enantioselectivities of up to 99% ee in these reactions by using related chiral $(NH)_2P_2$ macrocyclic iron complexes **6a** and **6b** readily tuned by modifying the substituents of their isonitrile ligands [17]. The transfer hydrogenation of a range of alkyl aryl ketones **2** performed in isopropanol at 50 or 60 °C in the presence of 1 mol% of $NaOt-Bu$ as a base and using in most cases only 0.1 mol% of catalyst **6a** ($R' = CEt_3$) or **6b** ($R' = N(i-Pr)_2$) led to the corresponding chiral alcohols **3** in moderate to quantitative yields (40–99%) and uniformly high enantioselectivities (86–99% ee), as shown in Scheme 3. The



Scheme 1. First enantioselective iron-catalyzed transfer hydrogenation of ketones [12].



Scheme 2. Chiral iron catalysts described by Morris, Gao and Mezzetti groups [13,14,16].

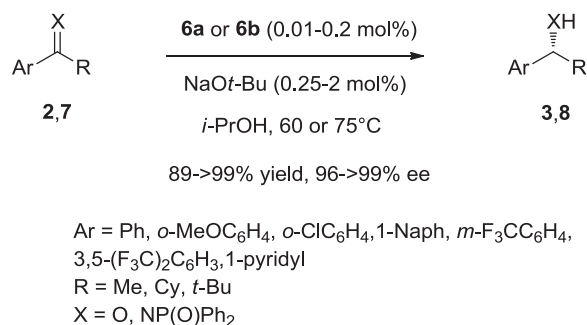


Ar = Ph, *p*-Tol, *m*-Tol, *o*-Tol, *p*-MeOC₆H₄, *m*-MeOC₆H₄, *o*-MeOC₆H₄, *p*-ClC₆H₄, *m*-ClC₆H₄, *o*-ClC₆H₄, 2-Naph, 1-Naph, *m*-F₃CC₆H₄, 3,5-(F₃C)₂C₆H₃, 1-pyridyl, 2-pyridyl, 3-pyridyl, 1-thienyl, 2-thienyl
R = Me, Et, *i*-Pr, Cy, *t*-Bu

Scheme 3. Transfer hydrogenation of alkyl aryl ketones catalyzed by chiral (NH)₂P₂ macrocyclic iron complexes [17].

scope of the process was large but alkyl aryl ketones bearing secondary or tertiary alkyl substituents (R = *i*-Pr, Cy, *t*-Bu) required a higher temperature (70 °C instead of 50–60 °C) and a higher catalyst loading (0.4 mol% instead of 0.1 mol%) to provide the corresponding alcohols with excellent enantioselectivities (97–98% ee).

In 2016, the same authors demonstrated that these reactions could be performed with lower catalyst loadings of only 0.01 mol % in some cases of substrates and lower quantities of base (0.25 mol%) [18]. As shown in Scheme 4, a series of chiral alkyl aryl

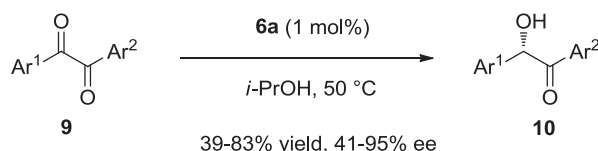


Scheme 4. Transfer hydrogenation of alkyl aryl ketones and a phosphinyl imine catalyzed by chiral (NH)₂P₂ macrocyclic iron complexes [18].

alcohols **3** was produced with both excellent yields (89→99%) and enantioselectivities (96→99% ee) from the corresponding ketones **2**. The scope of the process could also be extended to a phosphinyl imine (X = NP(O)Ph₂) **7** which afforded the corresponding enantiopure amine **8** (>99% ee) in 94% yield.

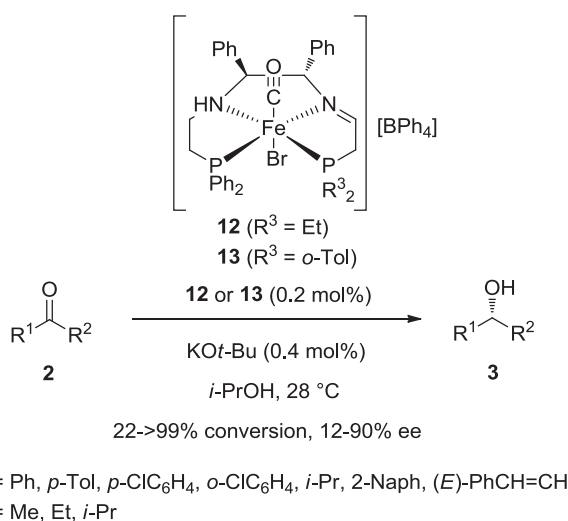
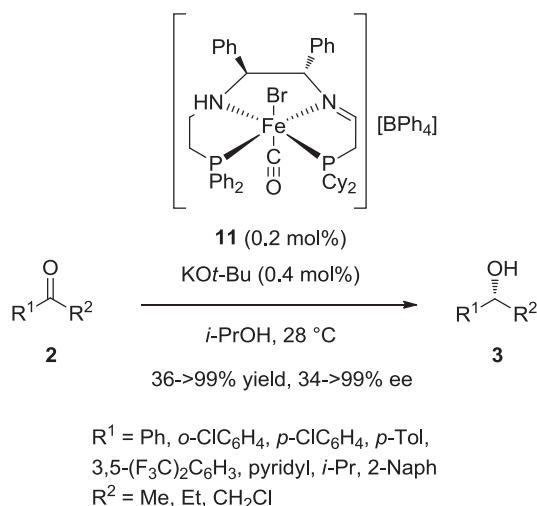
In these reactions, the presence of base additives, required to activate the precatalyst, limits the scope of the reaction. For example, α -hydroxy ketones whose base-labile stereocenter easily racemizes in basic media, render challenging the asymmetric hemihydrogenation of 1,2-diketones. In 2017, catalyst **6a** was successfully investigated by Mezzetti and De Luca to promote the base-free asymmetric transfer hydrogenation of this type of challenging substrates (Scheme 5) [19]. Indeed, the first asymmetric transfer hydrogenation of a range of benzyls **9** with isopropanol as a hydrogen source was performed in the presence of 1 mol% of catalyst **6a** at 50 °C, leading in the absence of base to the corresponding chiral benzoin **10** in both moderate to high yields (39–83%) and enantioselectivities (41–95% ee). The highest enantioselectivity (95% ee) was achieved in the reaction of unsubstituted benzoin (Ar¹ = Ar² = Ph) while *ortho*-substituted benzyls gave the corresponding alcohols with much lower enantioselectivities (41–62% ee).

Earlier in 2015, Morris reported the synthesis of a novel unsymmetrical chiral PNHNP' iron complex **11** to be applied in the asymmetric transfer hydrogenation of ketones [20]. As shown in Scheme 6, the asymmetric reduction of a range of ketones **2** was achieved in the presence of 0.2 mol% of catalyst **11** and 0.4 mol% of KO^{*t*}-Bu as a base in isopropanol at 28 °C, providing the corresponding chiral alcohols **3** in both moderate to excellent yields (36→99%) and enantioselectivities (34→99% ee). The reaction conditions were compatible to variously substituted alkyl aryl ketones but also to a dialkyl ketone (R¹ = *i*-Pr, R² = Me) the latter providing 50% yield and 43% ee. Later, related catalysts **12** and **13** bearing other phosphine substituents (R³ = Et, *o*-Tol) were investigated in



Ar¹ = Ph, *p*-MeOC₆H₄, *p*-FC₆H₄, *m*-MeOC₆H₄, *m*-FC₆H₄, *o*-FC₆H₄, *p*-BrC₆H₄
Ar² = Ph, *p*-MeOC₆H₄, *p*-FC₆H₄, *m*-MeOC₆H₄, *m*-FC₆H₄, *o*-FC₆H₄, *p*-ClC₆H₄, *p*-BrC₆H₄

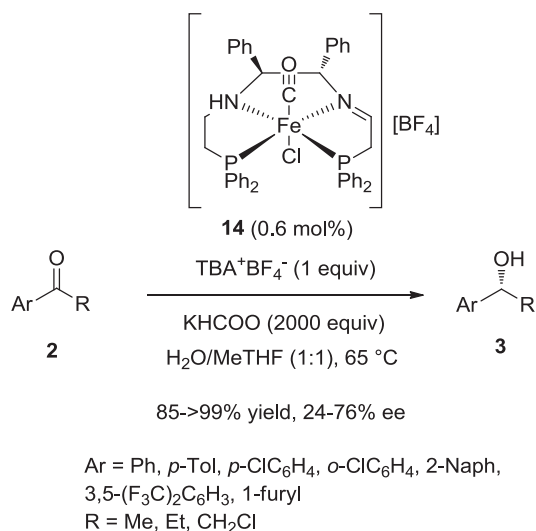
Scheme 5. Transfer hydrogenation of benzyls without base additive [19].



Scheme 6. Transfer hydrogenations of ketones catalyzed by unsymmetrical PNHNP' iron complexes [20,21].

these reactions under the same conditions in order to evaluate the role of the steric properties of the phosphine groups on the activity and enantioselectivity. The asymmetric transfer hydrogenation of a range of alkyl aryl and dialkyl ketones was achieved with low to complete conversions (22–>99%) and low to high enantioselectivities (12–90% ee), as shown in Scheme 6 [21]. The comparison of the results showed that by increasing the steric bulk at one phosphine ($\text{R}^3 = \text{Cy}$ or $o\text{-Tol}$ instead of Et), the enantioselectivity of the reaction increased.

The first iron-catalyzed asymmetric transfer hydrogenation of ketones performed under aqueous biphasic media was reported by the same authors, in 2016 [22]. It employed water and potassium formate as the proton and hydride source, respectively. The process was performed at 65 °C in the presence of a phase transfer catalyst, such as $\text{TBA}^+\text{BF}_4^-$, MeTHF as a cosolvent, and 0.6 mol% of chiral P-NH-N-P iron catalyst **14**. As shown in Scheme 7, the catalyst system was compatible to various alkyl aryl ketones **2**, leading to the corresponding chiral alcohols **3** in uniformly high yields (85–>99%) combined with low to moderate enantioselectivities (24–76% ee). In addition, another type of novel chiral iron catalysts, such as chiral N_2P_2 diferrocene iron complexes, were investigated by Zirakzadeh et al. in the asymmetric transfer hydrogenation of several alkyl aryl ketones albeit only low enantioselectivities ($\leq 29\%$ ee) were obtained [23].

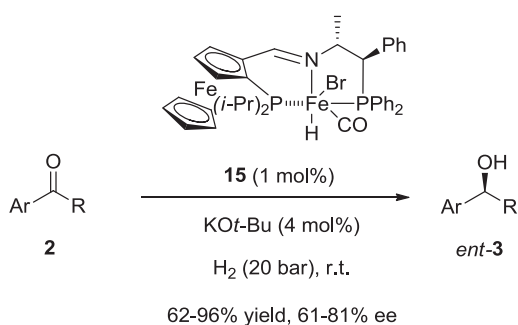


Scheme 7. Transfer hydrogenation of alkyl aryl ketones in aqueous biphasic media [22].

2.2. Asymmetric hydrogenations of ketones and imines

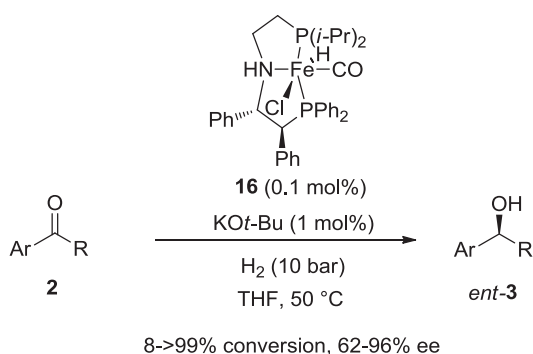
The direct asymmetric hydrogenation of ketones constitutes the most practical methodology to prepare chiral alcohols [24]. In contrast to precious metal-based catalysts commonly employed in these reactions, highly efficient enantioselective inexpensive metal catalysts are still rare. For example, the application of chiral iron catalysts in asymmetric hydrogenations is still very limited [3b,11f,h,25]. Early in 2008, Morris et al. reported enantioselectivities of 27% ee for the asymmetric hydrogenation of acetophenone by using a tetradentate N_2P_2 iron catalyst [13a]. Later in 2014, the same group reported higher enantioselectivities of up to 85% ee by using unsymmetrical PNP pincer ligands [26]. Ever since, other chiral iron catalysts have been applied to promote these reactions [27], among which a complex derived from a chiral hexadentate N_4P_2 macrocycle developed by Gao et al. in 2014, providing remarkable enantioselectivities of up to 99% ee [28]. More recently in 2016, Morris et al. reported the synthesis of novel chiral PNP' pincer ligands exhibiting a planar chiral ferrocene and a chiral aliphatic unit [29]. The corresponding chiral iron complexes derived from $\text{FeBr}_2(\text{THF})_2$ were investigated at room temperature in the asymmetric hydrogenation of various ketones in the presence of KOt-Bu as a base at a hydrogen pressure of 20 bar. A range of chiral alkyl aryl alcohols *ent*-**3** were obtained in moderate to excellent yields (62–96%) and moderate to good enantioselectivities (61–81% ee) by using 1 mol% of optimal catalyst **15**, as shown in Scheme 8.

In 2017, the same authors described the synthesis of a new family of chiral pincer PNHP' ligands and their iron catalysts to be applied in similar reactions [30]. These ligands were synthesized through reductive elimination of the corresponding chiral α -dialkylphosphine acetaldehydes. Among them, monohydride complex **16** employed at only 0.1 mol% of catalyst loading was found optimal promotor in the asymmetric hydrogenation of alkyl aryl ketones **2** performed in tetrahydrofuran at 50 °C at a hydrogen pressure of 10 bar (Scheme 9). Complete conversions (>99%) were obtained combined to uniformly excellent enantioselectivities (90–96% ee) for various ketones including challenging sterically hindered *o*-chloro-substituted ketone ($\text{Ar} = o\text{-ClC}_6\text{H}_4$, $\text{R} = \text{Me}$) which provided 93% ee. In only two cases of substrates, such as cyclohexyl phenyl ketone and 3',5'-bis(trifluoromethyl)acetophenone, low conversions (38% and 8%, respectively) were obtained



Ar = Ph, *p*-Tol, *p*-ClC₆H₄, *o*-ClC₆H₄, *p*-F₃CC₆H₄, *o*-FC₆H₄, *p*-MeOC₆H₄
R = Me, Et, Bn

Scheme 8. Hydrogenation of alkyl aryl ketones catalyzed by an iron catalyst derived from a chiral PNP' ligand [29].



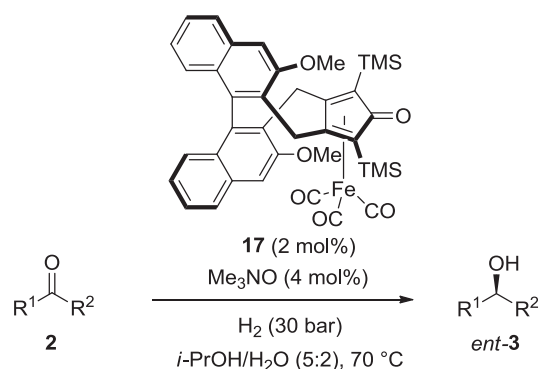
Ar = Ph, *o*-ClC₆H₄, 3,5-(F₃C)₂C₆H₃, *p*-ClC₆H₄, *p*-Tol,
2-Naph, 1-Naph, 2-furyl
R = Me, Et, Cy

Scheme 9. Hydrogenation of alkyl aryl ketones catalyzed by an iron catalyst derived from a chiral monohydride unsymmetrical PNHP' pincer ligand [30].

in combination with lower enantioselectivities (62% and 86% ee, respectively).

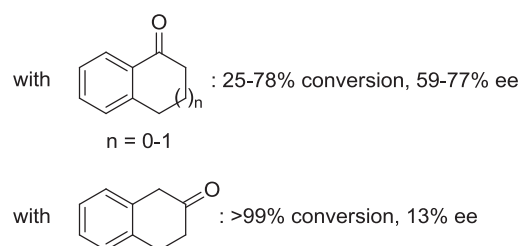
Earlier in 2015, Gennari et al. reported the synthesis of another type of chiral iron catalysts, such as chiral cyclopentadienone iron complexes derived from (*R*)-BINOL, to be investigated in these reactions [31]. In the presence of Me₃NO and hydrogen (30 bar) at 70 °C in a 5:2 mixture of isopropanol and water as a solvent, optimal complex **17** was in situ converted into the corresponding (hydroxycyclopentadienyl)iron hydride, which provided moderate to good enantioselectivities (46–77% ee) in the asymmetric hydrogenation of various ketones **2**, as shown in Scheme 10. The best enantioselectivities were achieved with the most hindered substrates albeit combined with low conversions. In addition to alkyl aryl ketones including cyclic ones, dialkyl ketones were also compatible, such as *t*-butyl methyl ketone which provided 77% ee and a conversion of 22%.

Other cyclopentadienone chiral iron complexes have been developed to be applied in these hydrogenations. For example, Renaud et al. have reported the synthesis of chiral cyclopentadienone iron tricarbonyl complexes, such as **18**, embedded in streptavidin [32]. As shown in Scheme 11, when 2.5 mol% of this first artificial iron hydrogenase was employed at 65 °C in the presence of 15 mol% of trimethylamine *N*-oxide in aqueous methanol as a solvent and at a hydrogen pressure of 30 bar, it allowed the asymmetric hydrogenation of *para*-methoxyacetophenone **2a** to be achieved in both low conversion (26%) and enantioselectivity (34% ee).

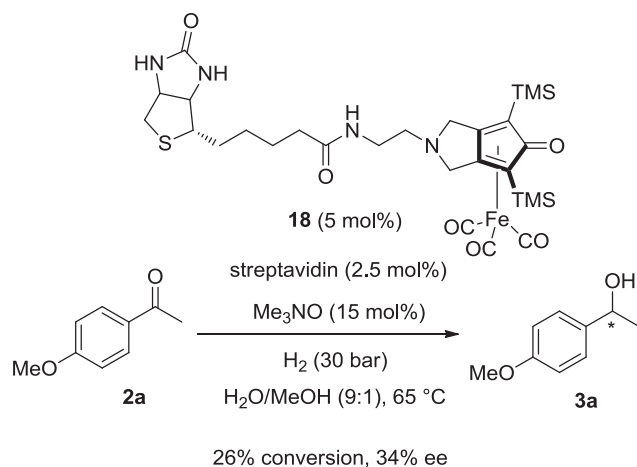


R¹ = *p*-F₃CC₆H₄, *p*-MeOC₆H₄, 1-Naph, pyridyl, Ph, Cy, *t*-Bu
R² = Me, Et

22->99% conversion, 46-77% ee



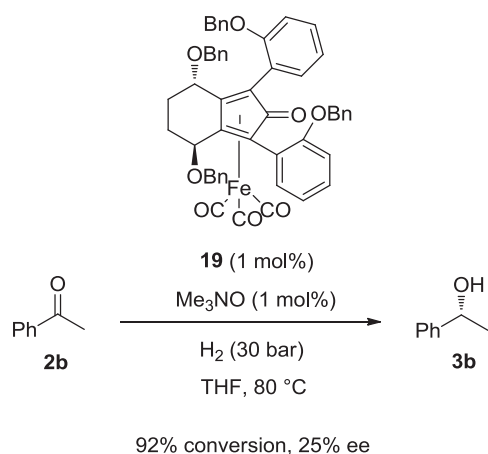
Scheme 10. Hydrogenation of ketones catalyzed by a chiral cyclopentadienone iron tricarbonyl complex [31].



Scheme 11. Hydrogenation of *para*-methoxyacetophenone catalyzed by a chiral cyclopentadienone iron tricarbonyl complex embedded in streptavidin [32].

In 2018, other chiral cyclopentadienone iron tricarbonyl complexes were designed by Wills et al. starting from a chiral 1,4-diol [33]. Among them, complex **19** employed at 1 mol% of catalyst loading in tetrahydrofuran at 80 °C in the presence of 1 mol% of trimethylamine *N*-oxide and hydrogen (30 bar) was found optimal catalyst to reduce acetophenone **2b** into **3b** with a high conversion (92%) albeit low enantioselectivity (25% ee), as shown in Scheme 12.

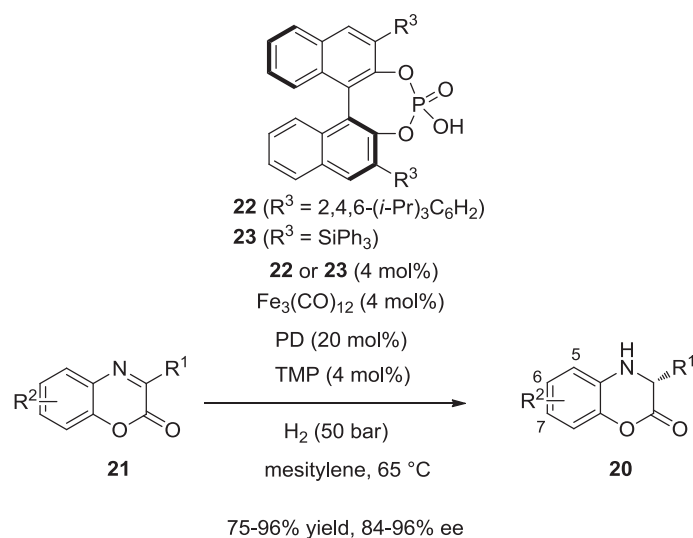
In another area, a different approach to asymmetric hydrogenation consists in using as a catalyst system a combination of an achiral metal catalyst with a chiral Brønsted acid [34]. For example in 2011, Beller et al. applied a combination of Knölker's complex [35] with a chiral BINOL-derived phosphoric acid, such as (*S*)-TRIP, to promote the asymmetric hydrogenation of acyclic and cyclic




Scheme 12. Hydrogenation of acetophenone catalyzed by another chiral cyclopentadienone tricarbonyl iron complex [33].

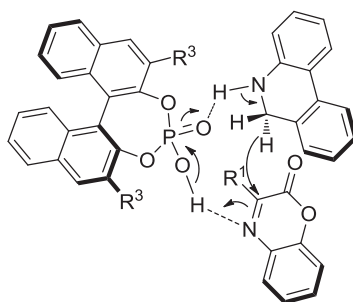
imines with excellent enantioselectivities of up to 98% ee [36]. Later in 2015, these authors reported the first example of asymmetric hydrogenation of benzoxazinones performed in the presence of a combination of a relay iron/chiral Brønsted acid

catalysis [37]. As shown in Scheme 13, a wide range of chiral 3-aryl and 3-alkyl substituted dihydrobenzoxazinones **20** could be synthesized in good to excellent yields (75–96%) and uniformly high enantioselectivities (84–96% ee) by catalyzing the hydrogenation of the corresponding benzoxazinones **21** with a combination of 4 mol% of $\text{Fe}_3(\text{CO})_{12}$ and the same quantity of chiral phosphoric acid **22** or **23** under a hydrogen pressure of 50 bar in mesitylene at 65 °C (Scheme 13). The process also employed 4 mol% of tris(4-methoxyphenyl)phosphane (TMP) as an achiral iron ligand and 20 mol% of phenanthridine (PD) as a cocatalyst. The authors have proposed a relay catalysis mechanism involving the generation of dihydrophenanthridine (DHPD) from phenanthridine in the presence of a catalytic amount of $\text{Fe}_3(\text{CO})_{12}$ and molecular hydrogen. Then, an asymmetric transfer hydrogenation underwent the selective reduction of the benzoxazinone by DHPD with cooperative participation of the chiral phosphoric acid (Scheme 13). This is the latter that was responsible of the control of the enantioselectivity through the possible hydride transfer process. Studying the scope of the reaction of 3-aryl substituted benzoxazinones, the authors found that benzoxazinones exhibiting electron-neutral, electron-deficient, electron-rich and sterically demanding substituents on the aryl ring as well as multiple substituents all smoothly led to the corresponding products in high yields (75–96%) and enantioselectivities (82–94% ee). Comparable excellent results (75–91%



R^1 = Ph, $p\text{-FC}_6\text{H}_4$, $p\text{-MeOC}_6\text{H}_4$, $p\text{-t-BuC}_6\text{H}_4$, 3,4- $\text{Me}_2\text{C}_6\text{H}_3$, Et, $i\text{-Pr}$, $n\text{-Bu}$, Bn, CH_2Bn , $i\text{-Hex}$, $(\text{CH}_2)_3\text{CH}=\text{CH}_2$, $(\text{CH}_2)_3\text{OMe}$, $(\text{CH}_2)_3\text{Cl}$, 
 R^2 = H, 7-F, 7-Cl, 7-Me, 7-OMe, 6-Me, 5-Me

proposed transition state:



Scheme 13. Hydrogenation of benzoxazinones catalyzed by a combination of $\text{Fe}_3(\text{CO})_{12}$ and chiral phosphoric acids [37].

yield, 86–96% ee) were also obtained in the reaction of a series of more challenging 3-alkyl substituted benzoxazinones. Interestingly, the catalyst system also tolerated many functional groups including alkene, methoxyl and chloride.

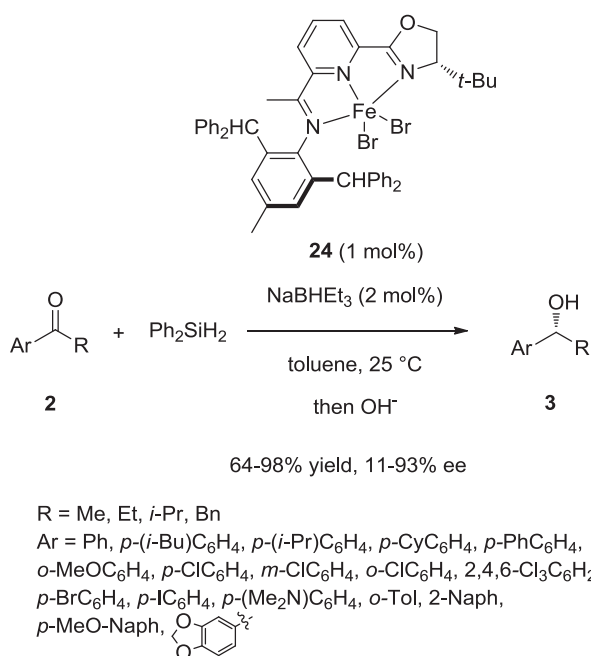
2.3. Asymmetric hydrosilylations of ketones

The enantioselective metal-catalyzed hydrosilylation of ketones constitutes an alternative to the asymmetric hydrogenation owing to its mild conditions and practicability [38]. A variety of chiral transition metal catalysts based on titanium, zinc, tin, copper and iron [11f] have been applied to promote these reactions with moderate to excellent enantioselectivities. Notably, the first enantioselective iron-catalyzed hydrosilylation of ketones with $(\text{EtO})_2\text{MeSiH}$ was reported by Nishiyama and Furuta, in 2007 [39]. It employed a combination of $\text{Fe}(\text{OAc})_2$ with chiral bis(oxazolinyl)phenylamine as a ligand, providing the corresponding alcohols in moderate to good enantioselectivities (57–79% ee). One year later, Beller et al. described enantioselectivities of up to 99% ee in the asymmetric hydrosilylation of ketones with $(\text{EtO})_3\text{SiH}$

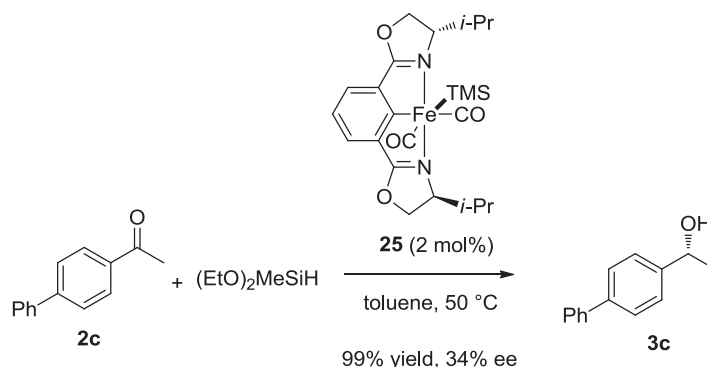
or polymethylhydrosiloxane as the reducing agent by using a chiral catalyst in situ generated from $\text{Fe}(\text{OAc})_2$ and $(S,S)\text{-Me-Duphos}$ as a ligand in the absence of any additives and activating agents [40]. Moreover, this remarkable catalyst system was compatible with a wide range of ketones, including diaryl and dialkyl ones. Later in 2015, Huang et al. reported the synthesis of novel chiral iminopyridine-oxazoline ligands to be investigated in related reactions [41]. As shown in Scheme 14, the optimal most sterically hindered catalyst **24**, preformed from the reaction of the corresponding ligand with FeBr_2 in tetrahydrofuran, allowed at 1 mol% of catalyst loading the asymmetric hydrosilylation of a range of alkyl aryl ketones **2** with Ph_2SiH_2 to be achieved at 25 °C in toluene in the presence of 2 mol% of NaBHET_3 . The corresponding chiral alcohols **3** were obtained in moderate to quantitative yields (64–98%) and low to excellent enantioselectivities (11–93% ee). The reaction worked efficiently for aromatic ketones bearing both electron-donating and electron-withdrawing groups (61–93% ee). The lowest enantioselectivities (11–24% ee) were obtained in the reaction of an aryl methyl ketone bearing an *ortho*-methoxy substituent on the phenyl ring ($\text{Ar} = o\text{-MeOC}_6\text{H}_4$, $\text{R} = \text{Me}$, 19% ee), a diaryl ketone ($\text{Ar} = o\text{-Tol}$, $\text{R} = \text{Ph}$, 24% ee) or benzyl methyl ketone ($\text{Ar} = \text{Ph}$, $\text{R} = \text{Bn}$, 11% ee). It was found that challenging dialkyl ketones provided even lower enantioselectivities (1–9% ee).

In the same year, Nishiyama and Ito described the synthesis of a series of novel NCN pincer chiral iron complexes containing silyl, stannyl, methyl and phenyl ligands to be evaluated in asymmetric hydrosilylation reactions [42]. Among them, silylated bis(oxazolinyl)phenyl iron complex **25** was found to be the most suitable catalyst to promote the reduction of *para*-phenyl acetophenone **2c** with $(\text{EtO})_2\text{MeSiH}$ in toluene at 50 °C. Even if the corresponding chiral alcohol **3c** was obtained in quantitative yield, the enantioselectivity of the reaction was low (34% ee), as shown in Scheme 15.

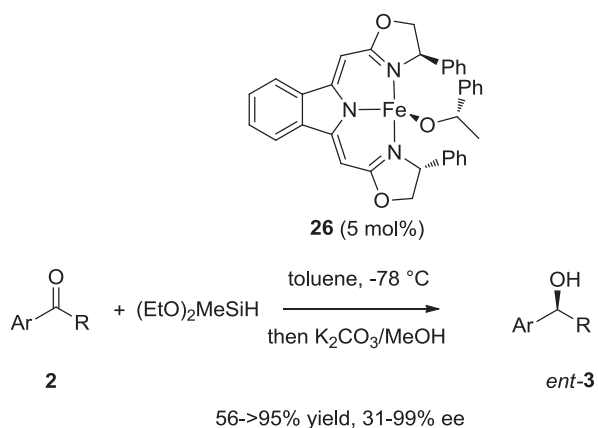
Later, Gade et al. reported the first asymmetric iron-catalyzed hydrosilylation of ketones providing enantioselectivity levels higher than 95% ee for a broad range of ketones [43]. These results were achieved by using 5 mol% of chiral bis(oxazolinyl)methylidene)isoindoline iron complex **26** in toluene at –78 °C and $(\text{EtO})_2\text{MeSiH}$ as a reducing agent. As shown in Scheme 16, a wide variety of alkyl aryl ketones **2** bearing substituents with varying electronic properties and steric bulk were compatible, giving the corresponding alcohols *ent*-**3** after subsequent treatment with K_2CO_3 in methanol in both moderate to excellent yields (56–>95%) and enantioselectivities (31–99% ee). In particular, substrates with long α -unbranched alkyl chains were reduced with high enantioselectivities (93–99% ee). Only a low enantioselectivity of 31% ee was observed in the reaction of a diaryl ketone ($\text{Ar} = \text{Ph}$, $\text{R} = p\text{-MeOC}_6\text{H}_4$). Besides the high stereoselectivity achieved, this catalyst system is certainly the most active iron-based hydrosilylation catalyst allowing catalytic reactions at low temperatures (–78 °C).



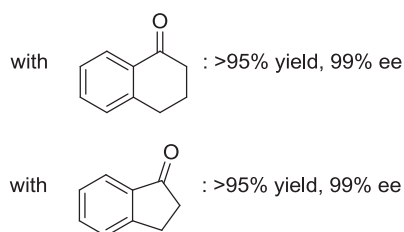
Scheme 14. Hydrosilylation of alkyl aryl ketones catalyzed by a chiral iminopyridine-oxazoline iron complex [41].



Scheme 15. Hydrosilylation of *para*-phenyl acetophenone catalyzed by a chiral bis(oxazolinyl)phenyl iron complex [42].



R = Me, Pr, *i*-Pr, *n*-Hex, *n*-C₁₁H₂₃, C₆F₅, *p*-MeOC₆H₄
 Ar = Ph, *p*-PhC₆H₄, *p*-MeOC₆H₄, *p*-MeO₂CC₆H₄, *p*-FC₆H₄, *p*-BrC₆H₄,
 4-(*t*-Bu)-2,6-Me₂C₆H₂, *o*-Tol, 1-Naph

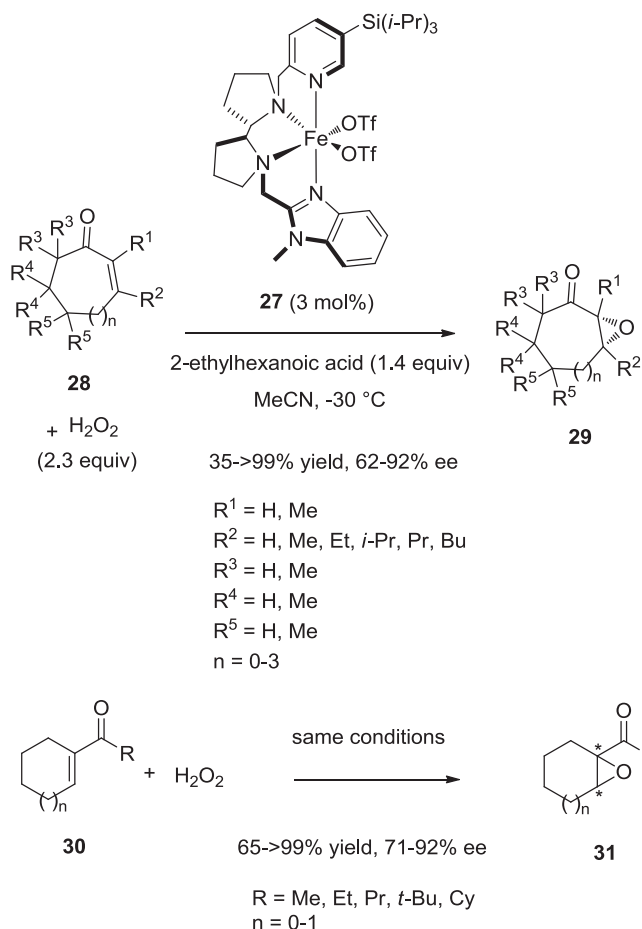


Scheme 16. Hydrosilylation of aromatic ketones catalyzed by a chiral bis(oxazolinylmethylidene)isoindoline iron complex [43].

3. Enantioselective epoxidations

3.1. Using H₂O₂ as an oxidant

Chiral epoxides represent pivotal building blocks in asymmetric organic synthesis [44]. In spite of important progress made in this field [45], performing epoxidation of alkenes by using iron complexes as catalysts and H₂O₂ as an oxidant instead of toxic or expensive reagents is highly desirable for economical and environmental reasons [3b]. In 2007, Beller et al. reported the first highly enantioselective iron-catalyzed epoxidation of olefins [46]. The process was catalyzed by a combination of FeCl₃(6H₂O) and chiral benzylamines as ligands in the presence of pyridine-2,6-dicarboxylic acid as an additive and H₂O₂ as an oxidant, providing the corresponding chiral epoxides with high enantioselectivities of up to 97% ee. Ever since, other types of chiral ligands have been developed to promote these reactions [8]. For example in 2016, Costas et al. investigated iron complexes of C₁-symmetric tetradentate N-based chiral ligands in the asymmetric epoxidation of cyclic α,β-unsaturated ketones with H₂O₂ [47]. The reaction was performed at -30 °C in acetonitrile as a solvent in the presence of 2-ethylhexanoic acid as an additive. The optimal catalyst was found to be **27** combining a bulky picoline, a benzimidazole ring and a chiral bipyrrrolidine. As shown in Scheme 17, a range of cyclic aliphatic α,β-unsaturated ketones **28** could be epoxidized by reaction with aqueous H₂O₂ to give the corresponding chiral epoxides **29** in both moderate to excellent yields (35->99%) and enantioselectivities (62-92% ee). Even challenging 2-cyclopentenone reacted with high yield (75%) and excellent enantioselectivity (90% ee), but a slight erosion of the enantioselectivity was observed when the enone ring was enlarged up to seven to eight member rings (84% and 81% ee, respectively). Moreover, it was found that substitutions at the olefinic side (α and β) decreased the enantioselectivity

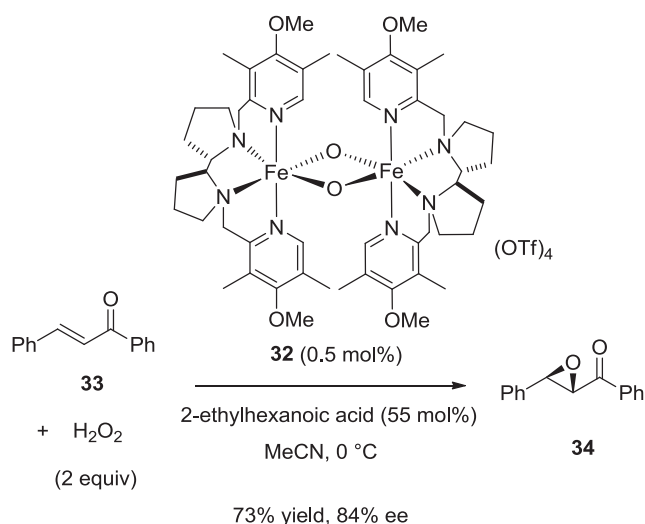


Scheme 17. Epoxidations of cyclic α,β-unsaturated ketones and cyclohexene- and cyclopentene-1-ketones catalyzed by a chiral picoline-benzimidazole-bipyrrrolidine iron complex [47].

ties (R¹ = Me, R² = R³ = R⁴ = R⁵ = H, n = 0-1, 62-65% ee), while substitutions at the opposite side (α' and β') led to their improvement. For example, particularly outstanding enantioselectivities (90-95% ee) were obtained in the reaction of substrates bearing a *gem*-dimethyl group in α' position. The scope of the methodology was extended to cyclohexene-1-ketones **30** (n = 1) which led under the same mild reaction conditions to the corresponding epoxides **31** in good to quantitative yields (65->99%) and high enantioselectivities (71-92% ee), as shown in Scheme 17. The highest enantioselectivities (87-92% ee) were obtained with substrates bearing different alkyl chains (R = Me, Et, Pr). For substrates bearing branched groups, such as *tert*-butyl and cyclopropyl, the enantioselectivities decreased slightly (74-80% ee). Moreover, the conditions were also compatible with a cyclopentene-1-ketone **30** (n = 0) albeit with lower enantioselectivity (71% ee), as shown in Scheme 17.

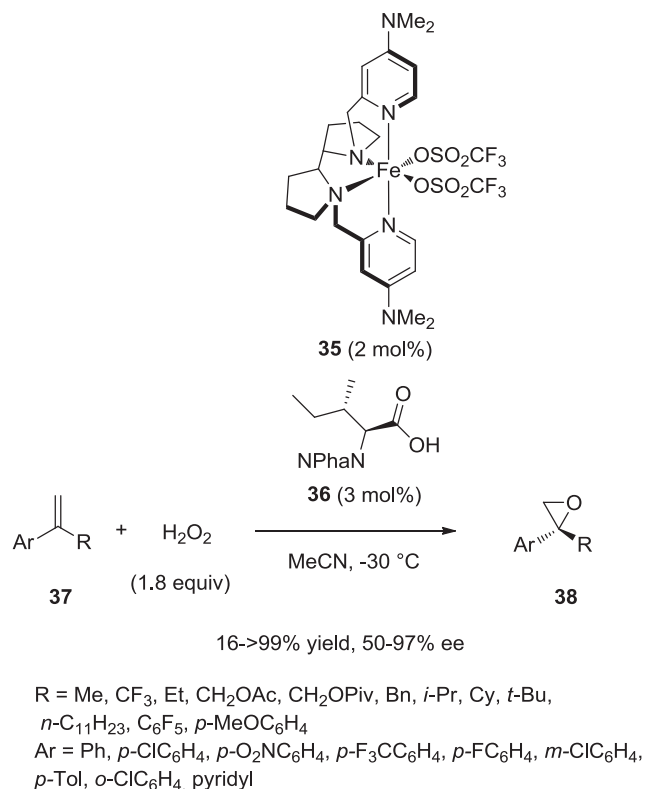
In 2012, Talsi et al. demonstrated that iron complexes of chiral tetradentate ligands based on the *N,N'*-bis(2-pyridylmethyl)-2,2'-bipyrrrolidine scaffold [48] were capable of epoxidizing electron-deficient olefins with high enantioselectivity by using H₂O₂ as an oxidant in the presence of a carboxylic acid as an additive [49]. Later in 2016, the same authors described the use of dinuclear *N,N'*-bis(2-pyridylmethyl)-2,2'-bipyrrrolidine catalyst **32** in the presence of 2-ethylhexanoic acid as an additive in acetonitrile at 0 °C to promote the asymmetric epoxidation of chalcone **33** into chiral epoxide **34** with H₂O₂ in 73% yield and 84% ee (Scheme 18) [50].

In the area of asymmetric epoxidation of non-activated alkenes, Costas et al. have described highly enantioselective epoxidation of



Scheme 18. Epoxidation of chalcone catalyzed by a chiral dinuclear *N,N'*-bis(2-pyridylmethyl)-2,2'-bipyrrrolidine) catalyst iron complex [50].

α -substituted styrenes catalyzed by 2 mol% of chiral bipyrrrolidine-derived aminopyridine iron complex **35** in the presence of 3 mol% of chiral *N*-protected amino acid **36** as a co-ligand [51]. *N*-Naphthalic anhydride (*N*-Pha) isoleucine **36** synergistically cooperated with the iron center in promoting an efficient activation of H_2O_2 to catalyze epoxidation of this challenging class of substrates. As shown in Scheme 19, the reaction of a wide range of α -substituted styrenes **37** with H_2O_2 in acetonitrile at -30°C led to the corresponding chiral epoxides **38** in low to quantitative yields (16–>99%) and moderate to excellent enantioselectivities (50–97% ee). The reaction of α -methylstyrene derivatives ($\text{R} = \text{Me}$) provided

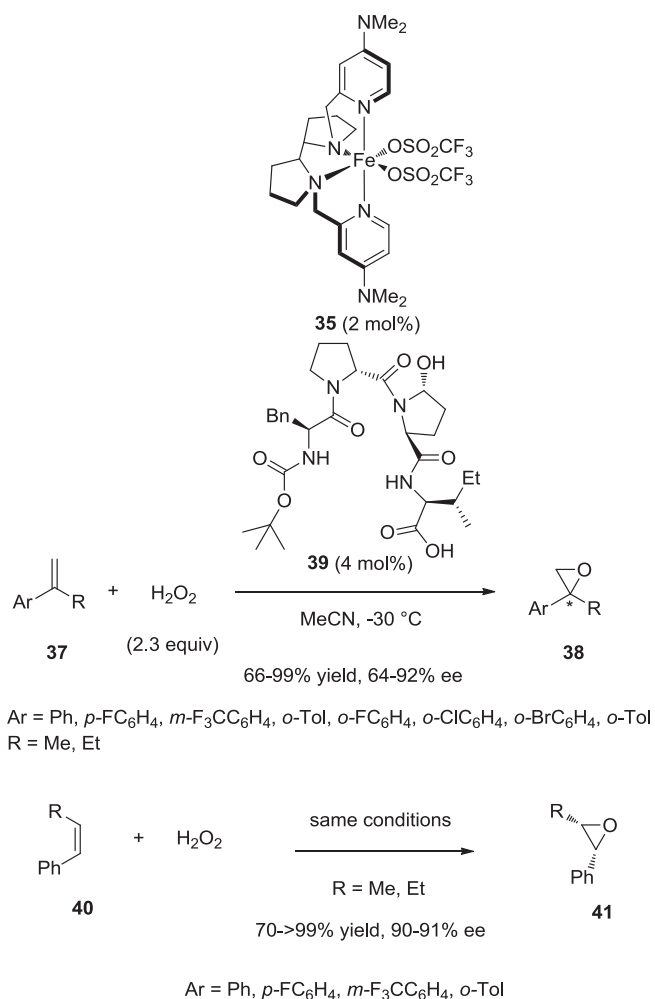


Scheme 19. Epoxidation of α -substituted styrenes catalyzed by a chiral bipyrrrolidine-derived aminopyridine iron complex in the presence of a chiral amino acid as a co-ligand [51].

excellent yields (88–94%) but moderate enantioselectivities (50–66% ee). On the other hand, replacing the α -methyl group by a sterically more demanding group, such as ethyl, isopropyl or *tert*-butyl, improved the enantioselectivities up to 97% ee. The system tolerated *ortho*-, *meta*- and *para*-substitutions of the aromatic ring, as well as different functional groups, such as nitro, esters and halides.

In the same area, chiral peptide **39** was combined with the same iron catalyst **35** to promote comparable asymmetric epoxidations of α -alkyl-substituted styrenes **37** [52]. As shown in Scheme 20, the corresponding chiral epoxides **38** were achieved in moderate to quantitative yields (66–99%) and moderate to high enantioselectivities (64–92% ee). The scope of this methodology was extended to *cis*-aromatic alkenes **40** which reacted with good to quantitative yields (70–>99%) to afford the corresponding chiral epoxides **41** in uniformly high enantioselectivities (90–91% ee), as shown in Scheme 20. This work that combined an iron center ligated to N and O based ligands with a peptide shaping the second coordination sphere of the metal, can be envisaged as a new approach towards artificial oxygenases.

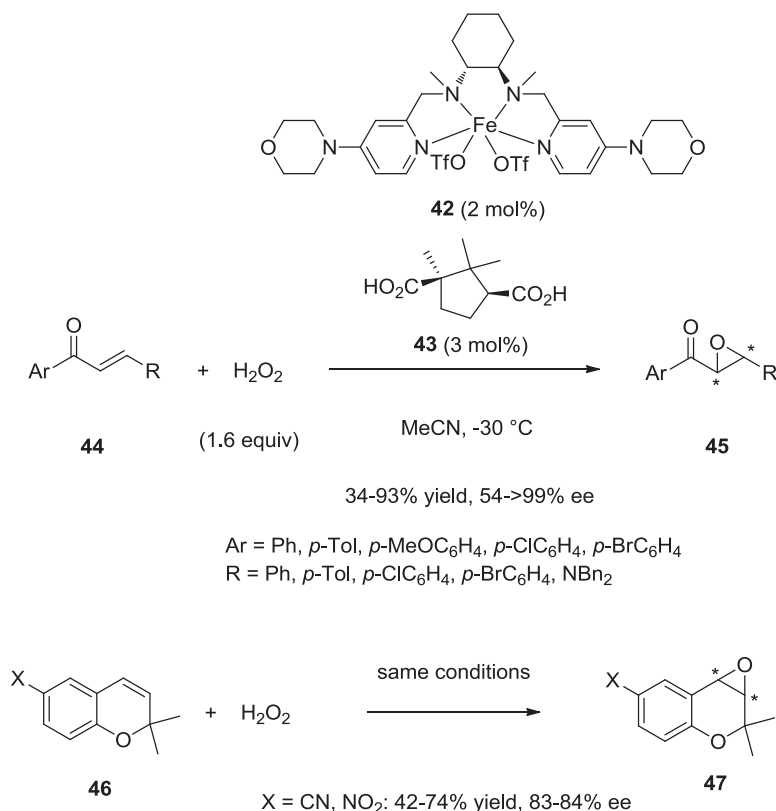
In 2017, Sun et al. reported the synthesis of novel iron complex **42** derived from a chiral aminopyridine N4 ligand bearing strong electron-donating and bulky morpholine groups [53]. This complex efficiently promoted the asymmetric epoxidation of various aromatic alkenes with H_2O_2 when combined with *D*-(+)-camphoric acid **43** as a chiral additive. As shown in Scheme 21, the asymmet-



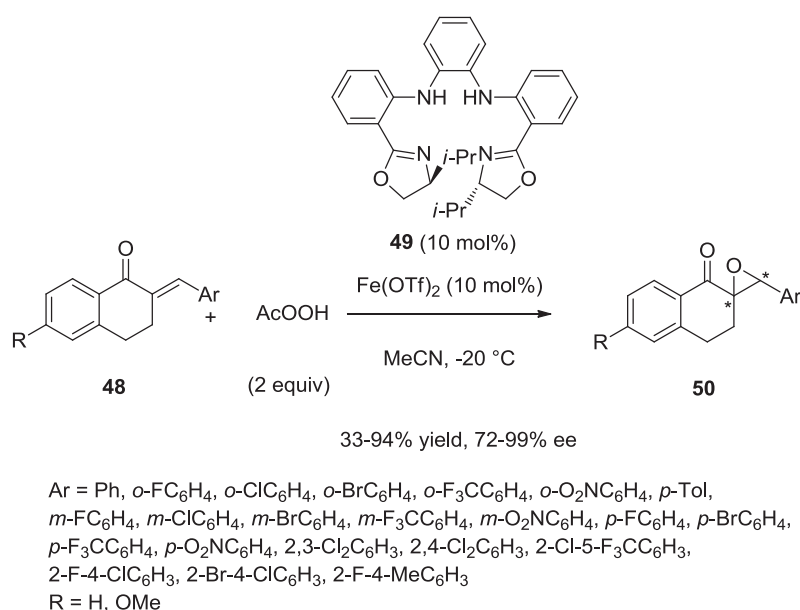
Scheme 20. Epoxidations of α -alkyl-substituted styrenes and *cis*-aromatic alkenes catalyzed by a chiral bipyrrrolidine-derived aminopyridine iron complex in the presence of a chiral peptide as a co-ligand [52].

ric epoxidation of various aromatic α,β -unsaturated ketones **44** performed at $-30\text{ }^{\circ}\text{C}$ in acetonitrile led to the corresponding epoxides **45** in both moderate to high yields (34–93%) and enantioselectivities (54–>99% ee). For example, chalcone derivatives with various electronic properties on the phenyl ring of the olefin reacted smoothly in excellent yields (80–93%) and enantioselectivities (90–94% ee). Only lower yields (41–62%) and enantioselectivities (72–83% ee) were obtained when either electron-donating or

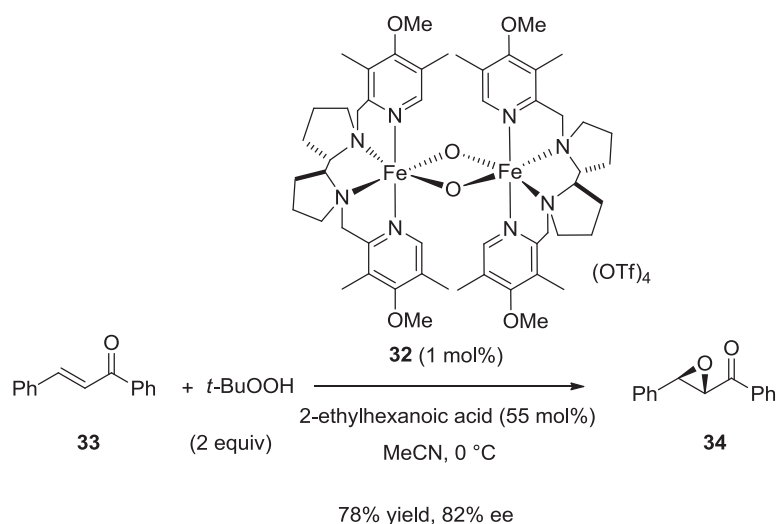
electron-withdrawing groups were introduced on the phenyl ring. The lowest result (34% yield, 54% ee) was obtained in the reaction of a disubstituted chalcone in both phenyl rings ($\text{Ar} = \text{R} = p\text{-ClC}_6\text{H}_4$). Interestingly, the catalyst system was compatible with electron-deficient alkenyl amides that afforded the corresponding epoxyamides in both excellent yields (90–91%) and enantioselectivities (91–>99% ee). As shown in Scheme 21, chromenes **46** were also tolerated, albeit providing the corresponding epoxides **47** in



Scheme 21. Epoxidations of various aromatic alkenes catalyzed by a chiral aminopyridine-morpholine N4 iron complex [53].



Scheme 22. Epoxidation of acyclic α,β -unsaturated aromatic ketones by using peracetic acid as an oxidant catalyzed by a chiral iron catalyst derived from a porphyrin-inspired ligand [54].



Scheme 23. Epoxidation of chalcone by using *tert*-butyl hydroperoxide as an oxidant catalyzed by a chiral binuclear bipyrrolidine-derived aminopyridine iron complex [56].

moderate to good yields (42–74%) combined with good enantioselectivities (83–84% ee).

3.2. Using peracids or hydroperoxides as oxidants

In 2015, Gao et al. reported iron-catalyzed asymmetric epoxidations of electron-deficient olefins **48** by using peracetic acid as an oxidant [54]. The process was promoted by 10 mol% of a chiral catalyst in situ generated from $\text{Fe}(\text{OTf})_2$ and chiral porphyrin-inspired ligand **49** in acetonitrile at -20°C . As shown in Scheme 22, it pro-

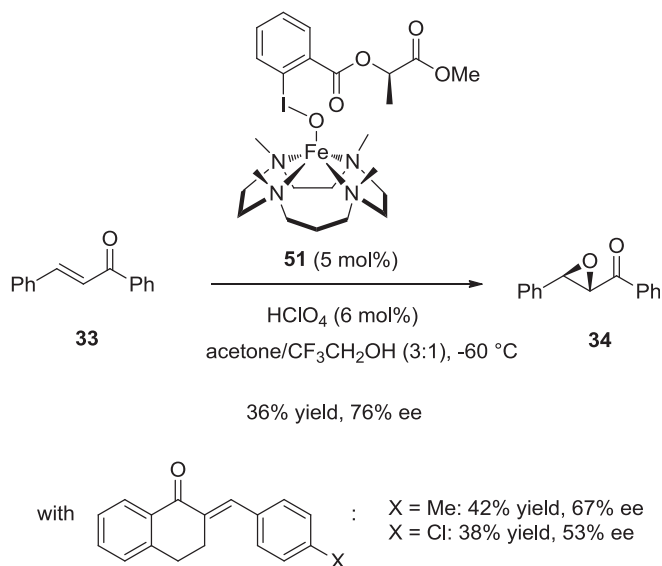
vided a range of highly enantioenriched α,β -epoxyketones **50** in low to excellent yields (33–94%) and good to excellent enantioselectivities (72–99% ee). The same reaction conditions could be applied to the asymmetric epoxidation of a chalcone derivative, giving the corresponding chiral epoxide in 92% yield albeit with a moderate enantioselectivity (63% ee). Moreover, the authors later demonstrated that the same catalyst system was compatible under continuous flow, providing moderate to high yields (52–90%) and enantioselectivities (63–92% ee) [55].

In 2017, Bryliakov and Talsi reported the asymmetric epoxidation of chalcone **33** by using *tert*-butyl hydroperoxide as an oxidant catalyzed by 1 mol% of chiral binuclear bipyrrolidine-derived aminopyridine iron complex **32** [56]. As shown in Scheme 23, the reaction was performed at 0°C in the presence of 2-ethylhexanoic acid as an additive in acetonitrile as a solvent, leading to the corresponding chiral epoxide **34** in 78% yield and 82% ee.

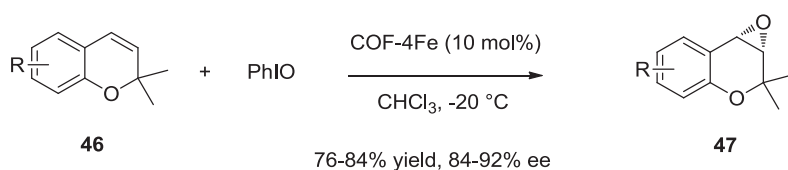
3.3. Using PhIO as an oxidant

In 2015, Nam et al. investigated in situ generated iron-iodosylbenzene complexes as catalysts in the asymmetric epoxidation of chalcone **33** [57]. As shown in Scheme 24, when the epoxidation of chalcone was catalyzed by 5 mol% of chiral spectroscopically well-characterized non-heme iron(III)-iodosylarene complex **51** in the presence of perchloric acid at -60°C , it afforded the corresponding epoxide **34** in moderate yield (36%) and good enantioselectivity (76% ee). These conditions were also applied to other substrates, such as tetralones, albeit with lower enantioselectivities (53–67% ee).

In 2017, Cui and Liu reported the asymmetric epoxidation of alkenes catalyzed by a heterogeneous iron complex derived from covalent chiral organic frameworks [58]. The latter were synthesized through metal-directed imine-condensations of enantiopure 1,2-diaminocyclohexane with C_3 -symmetric tris(allyl)aldehydes having one or zero 3-*tert*-butyl groups. As shown in Scheme 25,



Scheme 24. Epoxidation of chalcone and 2-(benzylidene)-1-tetralones catalyzed by a chiral non-heme iron(III)-iodosylarene complex [57].



Scheme 25. Epoxidation of chromenes catalyzed by a chiral heterogeneous iron complex derived from covalent organic framework [58].

using 10 mol% of these Zn(salen)-based chiral organic frameworks COF-4Fe in chloroform at $-20\text{ }^{\circ}\text{C}$ allowed the asymmetric epoxidation of chromenes **46** with PhIO to give the corresponding chiral tricyclic products **47** in both high yields (76–84%) and enantioselectivities (84–92% ee).

4. Additions to alkenes

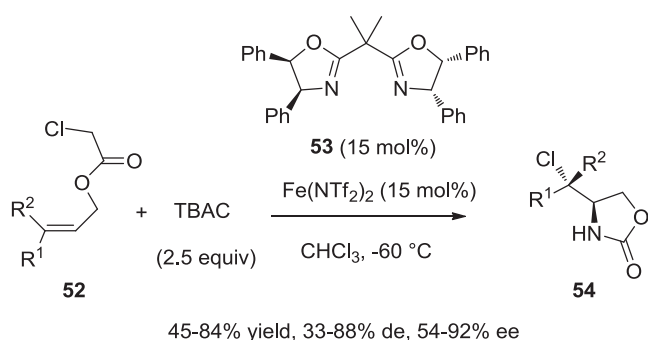
Asymmetric halo-functionalization reactions of alkenes allow chiral synthetically useful functionalized compounds to be easily synthesized [59]. While many asymmetric olefin halo-oxygenation reactions have been described, much fewer asymmetric olefin aminohalogenation methodologies are available. Especially, asymmetric aminochlorination reactions of alkenes are still very rare. To address this issue, Xu et al. recently developed an iron-catalyzed diastereo- and enantioselective intramolecular aminochlorination of alkenes **52** with tetra-*n*-butylammonium chloride (TBAC) [60]. As shown in Scheme 26, the process was cat-

alyzed by a chiral iron catalyst in situ generated from 15 mol% of $\text{Fe}(\text{NTf}_2)_2$ and the same quantity of chiral bisoxazoline **53** in chloroform at $-60\text{ }^{\circ}\text{C}$. It regioselectively led to a range of chiral *anti*-products **54** in moderate to good yields (45–84%) combined with moderate to high diastereo- and enantioselectivities (33–88% de and 54–92% ee, respectively), as shown in Scheme 26. In most cases of substrates studied, the enantioselectivities were high (77–92% ee) spanning from disubstituted styrenyl olefins bearing various substituents on the phenyl ring to extended aromatic derivatives including naphthyl olefins.

The enantiomeric catalyst system was applied by these authors to promote the asymmetric intramolecular aminobromination of isomeric alkenes **55** with tetraethylammonium bromide (TEAB) [61]. As shown in Scheme 27, using the same quantity of precatalyst $\text{Fe}(\text{NTf}_2)_2$ and chiral bisoxazoline ligand *ent*-**53** in dichloromethane at $-60\text{ }^{\circ}\text{C}$, the reaction of *trans*-alkene **55** led to the corresponding chiral *anti*-bromo amine **56** in good yield (64%) and both high diastereo- and enantioselectivities (90% de, 89% ee). On the other hand, the *cis*-olefin **55** reacted less-stereoselectively since a mixture of *anti*- and *syn*-diastereomers **56** and **57** were obtained in 53% yield, 66% de and 77% ee.

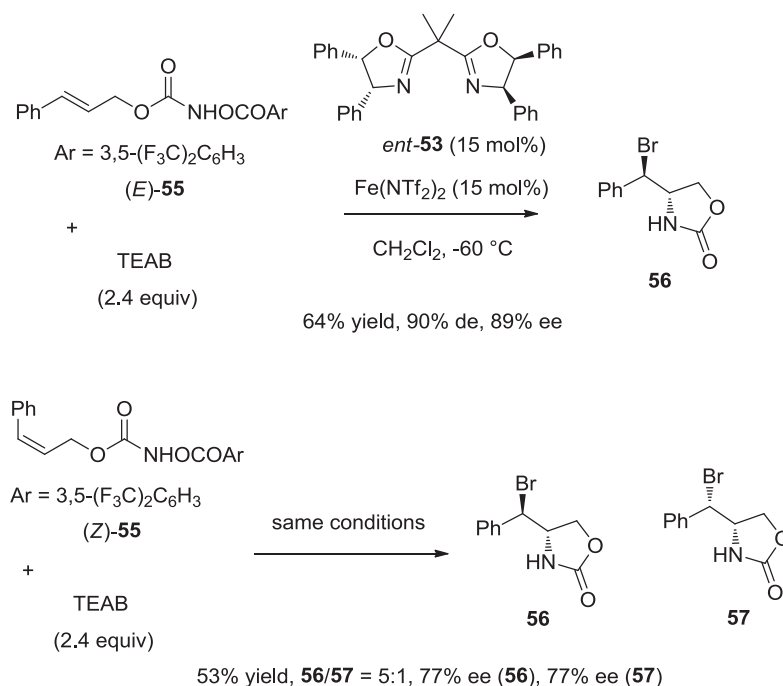
Later, the same authors developed enantioselective iron-catalyzed intermolecular aminofluorination of indene **58** performed in the presence of carbamates **59** and a mixture of XtalFluor-E and TEA(3THF) as a fluorination agent [62]. The reaction was performed at -35 to $0\text{ }^{\circ}\text{C}$ in a mixture of dichloromethane and acetonitrile as a solvent. The chiral iron catalyst was in situ generated from 20 mol% of $\text{Fe}(\text{NTf}_2)_2$ and 20 mol% of chiral pybox ligand **60**, yielding regioselectively a range of chiral functionalized indenenes **61** in moderate yields (35–59%), moderate *anti*-diastereoselectivities (38–68% de) and moderate to good enantioselectivities (32–84% ee), as shown in Scheme 28.

In 2016, another type of ligands, such as chiral *N,N'*-dioxides, was investigated by Feng and Liu in enantioselective iron-catalyzed intramolecular haloetherifications of α,β -unsaturated ketones [63]. For example, the intramolecular chloroetherification of a variety of activated olefins **62** with *p*-NsNCl₂ as a chlorine source was optimally catalyzed by 5 mol% of a chiral iron catalyst



$\text{R}^1 = \text{Ph}, p\text{-Tol}, p\text{-MeO}_2\text{C}_6\text{H}_4, p\text{-FC}_6\text{H}_4, p\text{-ClC}_6\text{H}_4, p\text{-BrC}_6\text{H}_4, m\text{-Tol}, m\text{-ClC}_6\text{H}_4, m\text{-BrC}_6\text{H}_4, o\text{-Tol}, o\text{-ClC}_6\text{H}_4, 1\text{-Naph}, 2\text{-Naph}, \text{Cy}$
 $\text{R}^2 = \text{H}, \text{Me}$

Scheme 26. Intramolecular aminochlorination of alkenes [60].

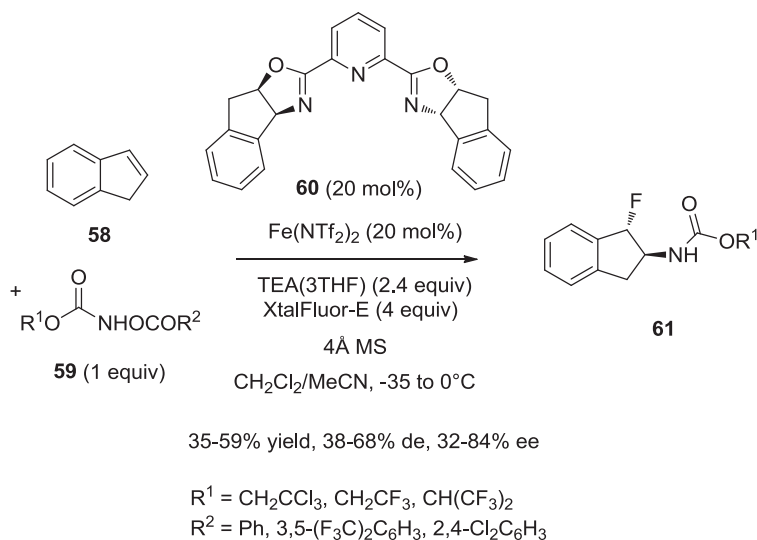


Scheme 27. Intramolecular aminobrominations of isomeric alkenes [61].

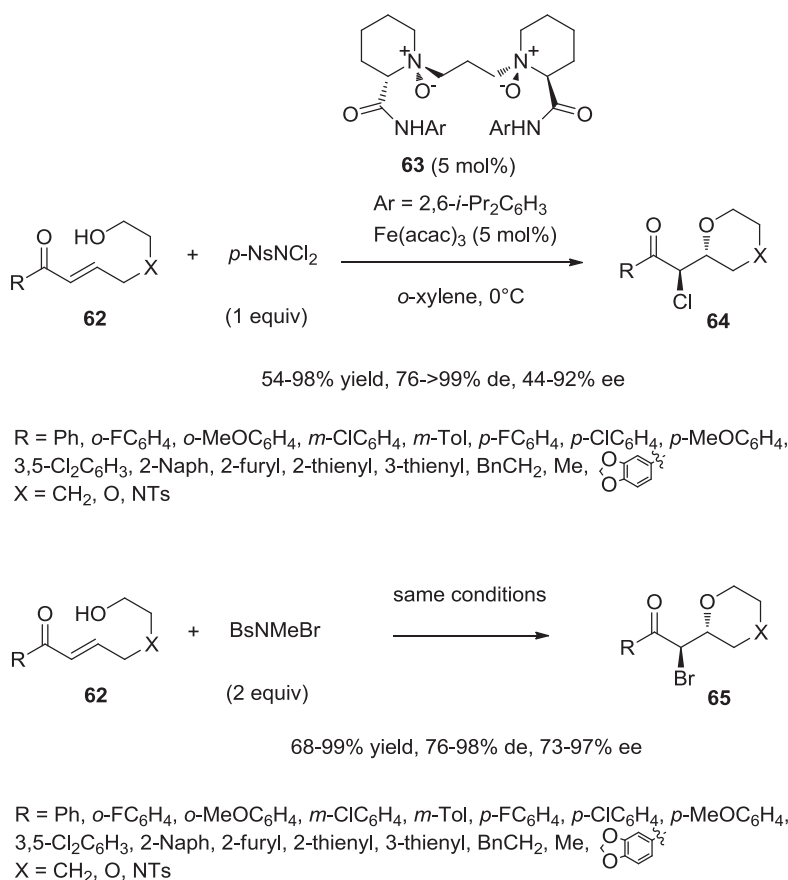
in situ generated from $\text{Fe}(\text{acac})_3$ and chiral N,N' -dioxide ligand **63**, as shown in Scheme 29. It led to the corresponding chiral *anti*-products **64** in moderate to quantitative yields (54–98%), good to excellent diastereoselectivities (76–>99% de) and moderate to excellent enantioselectivities (44–92% ee). The same conditions could be applied to the asymmetric intramolecular bromoetherification of α,β -unsaturated ketones **62** by using BsNMeBr as a bromine source (Bs = benzenesulfonyl). In this case, the

corresponding *anti*-products **65** were obtained in comparable diastereoselectivities (76–98% de) albeit combined with better enantioselectivities (73–97% ee) and slightly higher yields (68–99%), as shown in Scheme 29. The utility of this methodology was demonstrated in a total synthesis of the biologically active natural product (–)-centrolobine.

Another N,N' -dioxide ligand **66** was later applied at only 0.5 mol % of catalyst loading by the same authors to the asymmetric iron-



Scheme 28. Intermolecular aminofluorination of indene [62].

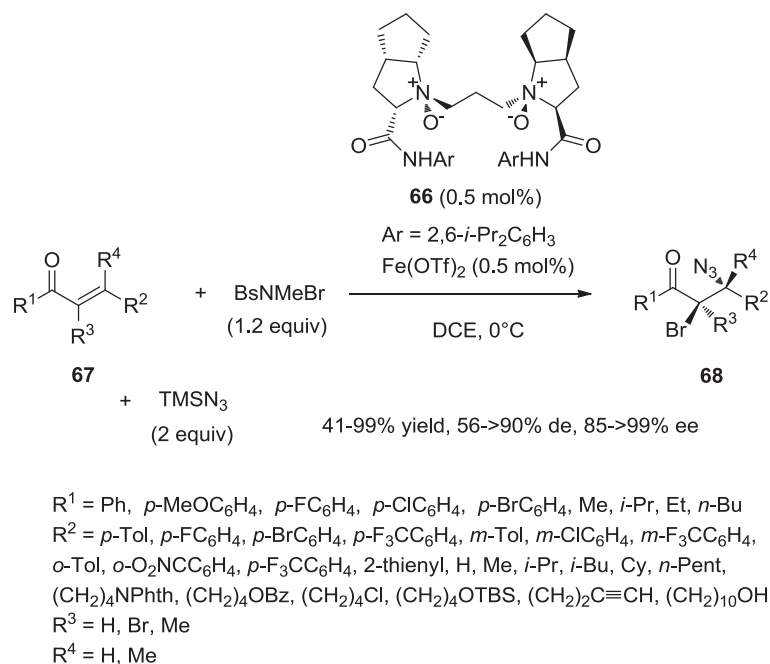


Scheme 29. Intramolecular chloroetherification and bromoetherification of activated alkenes [63].

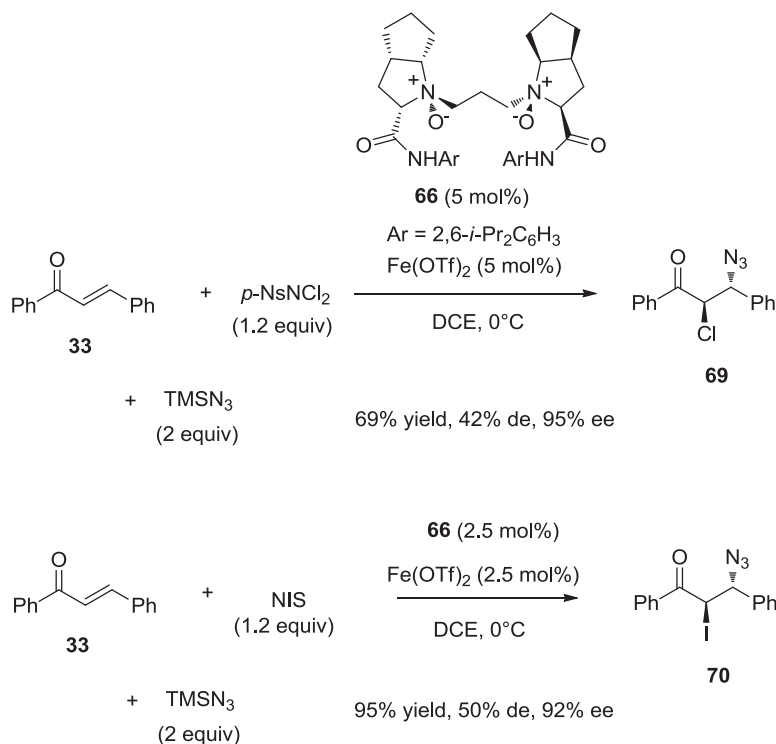
catalyzed bromoazidation of α,β -unsaturated ketones **67** [64]. The catalyst was in situ generated from 0.5 mol% of $\text{Fe}(\text{OTf})_2$ and ligand **66** in dichloroethane at 0 °C. The three-membered reaction of a wide range of activated alkenes **67** with BsNMeBr and TMSN_3 afforded the corresponding chiral α -bromo- β -azido ketones **68** in moderate to quantitative yields (41–99%), moderate to high *anti*-diastereoselectivities (56–>90% de) and high enantioselectivities (85–>99% ee), as shown in Scheme 30. The scope of this novel process was wide since it included aryl, heteroaryl and alkyl substi-

tuted α,β -unsaturated ketones. It represented the first highly diastereo- and enantioselective iron-catalyzed haloazidation of α,β -unsaturated ketones.

The same catalytic system was also applicable to the chloroazidation and iodoazidation of chalcone **33**, as depicted in Scheme 31 [64]. The reactions required higher catalyst loadings of 5 mol% and 2.5 mol%, respectively. The chloroazidation of chalcone with *p*- NsCl_2 as a chloride source and TMSN_3 as an azidation agent led to the corresponding chiral product **69** in good yield (69%) and high



Scheme 30. Bromoazidation of α,β -unsaturated ketones [64].



Scheme 31. Chloroazidation and iodoazidation of chalcone [64].

enantioselectivity (95% ee) albeit combined with moderate *anti*-diastereoselectivity (42% de). Similarly, the three-membered reaction between chalcone **33**, TMSN₃ and NIS as an iodine source afforded the corresponding *anti*-product **70** in both excellent yield (95%) and enantioselectivity (92% ee) combined with a moderate diastereoselectivity (50% de), as shown in [Scheme 31](#).

In another area, highly enantioselective iron-catalyzed *cis*-dihydroxylations of alkenes using H₂O₂ as an oxidant were developed by Che et al., in 2016 [\[65\]](#). These reactions were catalyzed by 3 mol% of tetradentate N4 iron complex **71** in methanol at -27 °C. As shown in [Scheme 32](#), excellent results were achieved in the reaction of a broad range of (*E*)-alkenes **72** since uniformly high enantioselectivities (87–>99% ee) combined with good to quantitative yields (68–>99%) were obtained for the corresponding *cis*-diols **73**. The catalyst system was also applicable to a (*Z*)-alkene **74**, which provided the corresponding *cis*-diol **73a** albeit with both lower yields (21–81%) and enantioselectivities (22–83% ee), as shown in [Scheme 32](#).

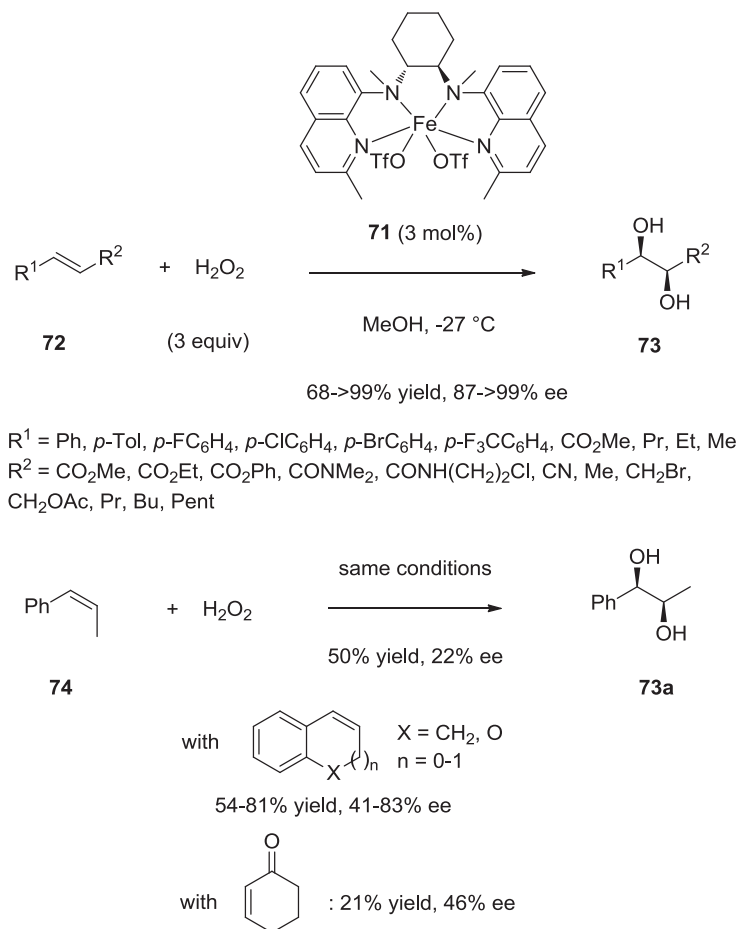
In another context, chiral iron complexes have also been employed to promote asymmetric hydrosilylations of alkenes, providing a direct access to pivotal chiral organosilanes [\[66\]](#). In 2015, Lu et al. described the first highly regio- and enantioselective iron-catalyzed anti-Markovnikov hydrosilylation of 1,1-disubstituted aryl alkenes **75** [\[67\]](#). As shown in [Scheme 33](#), the reaction employed Ph₂SiH₂ as a silylating agent and was catalyzed at room temperature by 1–5 mol% of tridentate N3 chiral iron complex **76** in the presence of NaBHET₃ as a reducing agent in toluene or even without solvent. The reaction of a wide range of 1,1-disubstituted aryl alkenes **75** led to the corresponding chiral organosilanes **77** in good to quantitative yields (64–99%) and

uniformly high enantioselectivities (78–>99% ee), as shown in [Scheme 33](#). On the other hand, much lower enantioselectivities (5–11% ee) were obtained in the reaction of aliphatic 1,1-disubstituted alkenes.

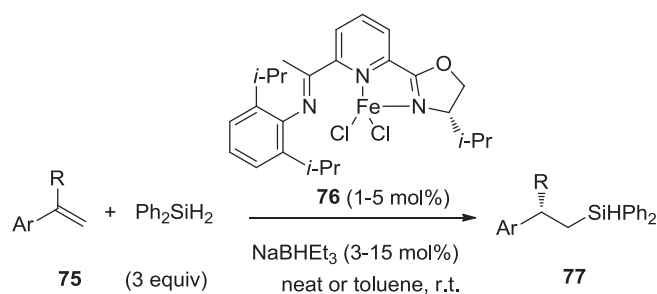
In 2017, the same authors applied a related catalyst system to achieve the first stereospecific iron-catalyzed hydroboration of vinylcyclopropanes with HBPin [\[68\]](#). The chiral iron catalyst **78** enabled the efficient and regioselective C–C cleavage of the racemic *trans*-vinylcyclopropanes, stereoselectively affording the corresponding chiral *E*-alkenes with good stereospecificity selectivity at the allylic position. As shown in [Scheme 34](#), the Markovnikov-selective reaction of a range of racemic *trans*-vinylcyclopropanes **79** led to the corresponding chiral homoallylic organoboronic esters **80** in moderate to excellent yields (39–97%) and high enantioselectivities (77–90% ee).

5. Enantioselective nucleophilic additions to carbonyl compounds and derivatives

In 2015, Feng et al. reported the use of 5 mol% of a chiral iron catalyst to promote the asymmetric intramolecular Cannizzaro reaction of a range of aryl and alkyl glyoxal monohydrates [\[69\]](#). The catalyst was in situ generated from FeCl₃ and chiral *N,N'*-dioxide **66** in dichloromethane as a solvent. As shown in [Scheme 35](#), the reaction of aryl and alkyl glyoxals **81** with various alcohols provided the corresponding chiral α-hydroxy esters **82** in moderate to quantitative yields (49–99%) and good to excellent enantioselectivities (75–97% ee). The best enantioselectivities were generally obtained when using sterically hindered alcohols, such as *tert*-butanol.

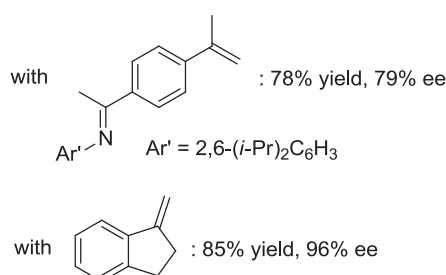


Scheme 32. *Cis*-Dihydroxylations of (*E*)- and (*Z*)-alkenes with H₂O₂ [\[65\]](#).



64–99% yield, 78–>99% ee

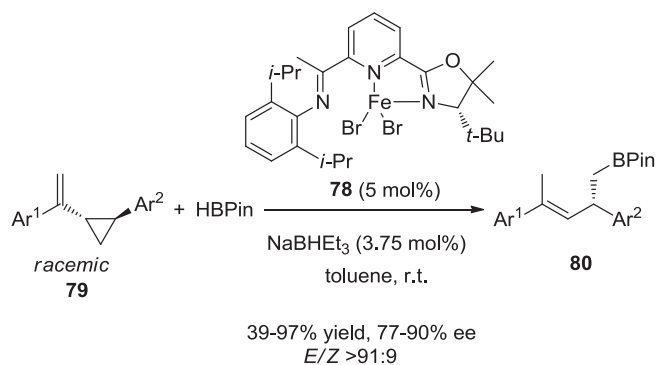
Ar = Ph, *p*-Tol, *m*-Tol, *o*-Tol, *p*-FC₆H₄, *p*-*i*-BuC₆H₄, *p*-Me₂NC₆H₄,
p-FC₆H₄, *m*-FC₆H₄, *o*-FC₆H₄, *o*-ClC₆H₄, *p*-MeOC₆H₄, *o*-MeOC₆H₄,
o-F₃CC₆H₄, 2-Naph, 1-Naph
R = Me, *n*-Pr, *n*-Hex, *i*-Pr, *i*-Bu, Cy, (CH₂)₃OTBS



Scheme 33. Hydrosilylation of 1,1-disubstituted aryl alkenes [67].

In another context, enantioselective iron-catalyzed hydrophosphonylations of aldehydes were developed by Li and Xu, in 2015 [70]. Among novel chiral camphor Schiff base iron ligands designed to promote these reactions, chiral ligand **83** was found optimal when employed at 10 mol% of catalyst loading in combination with FeCl₃ as a precatalyst. As shown in Scheme 36, the asymmetric hydrophosphonylation of a wide variety of aromatic and aliphatic aldehydes **84** with HPO(OEt)₂ led at room temperature in the presence of NaHCO₃ as a base in tetrahydrofuran as a solvent to the corresponding chiral alcohols **85** in high yields (73–91%) and moderate to good enantioselectivities (41–82% ee). The lowest enantioselectivity of 41% ee was obtained in the reaction of an aliphatic aldehyde.

In 2017, Mlynarski and Dudek reported the first enantioselective addition of nitroalkanes to imines mediated by a chiral iron



Ar¹ = Ph, *p*-Tol, *p*-MeOC₆H₄, *p*-Me₂NC₆H₄, *m*-FC₆H₄
Ar² = Ph, *p*-MeOC₆H₄, *p*-ClC₆H₄, 2-Naph

Scheme 34. Hydroboration of vinylcyclopropanes [68].

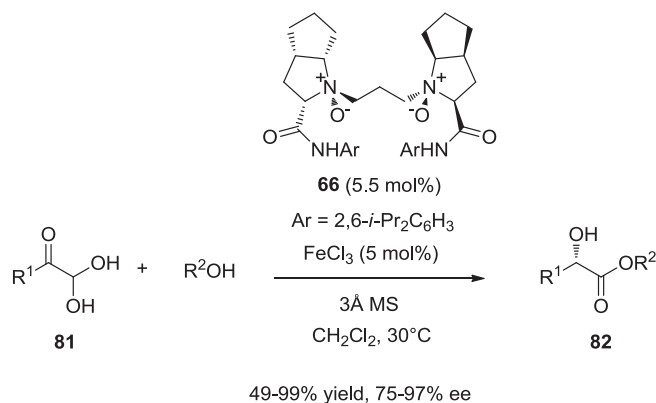
catalyst (Scheme 37) [71]. The latter was in situ generated in tetrahydrofuran at room temperature from 5 mol% of Fe(OTf)₂ and the same quantity of chiral sterically hindered pybox ligand **86**. The asymmetric nitro-Mannich reaction of a range of *N*-phosphinoyl-protected (hetero)aryl imines **87** with nitromethane **88a** (R = H) afforded in the presence of TEA as a base the corresponding chiral β-nitro amines **89** in moderate to high yields (52–91%) and uniformly very high enantioselectivities (89–98% ee). The scope was extended to higher order nitroalkanes (R ≠ H) with comparable enantioselectivities (89–90% ee) albeit combined with lower yields (40–61%) and without diastereoselectivity.

Chiral iron N₂P₂ dicationic complexes developed by Mezzetti et al. were investigated to promote the asymmetric Strecker reaction of azomethine imines **90** [72]. As shown in Scheme 38, the use of 10 mol% of catalyst **91** to promote these reactions in dichloromethane at –25 °C provided the corresponding chiral nitriles **92** in uniformly high yields (82–99%) albeit with low enantioselectivities (17–22% ee).

6. Enantioselective sulfa-Michael additions

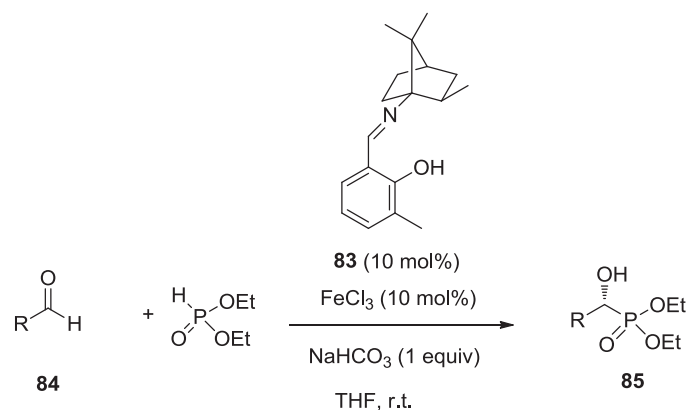
Michael additions of nucleophiles to electron-poor alkenes allow carbon–carbon and carbon–heteroatom bond-forming reactions to be easily achieved [73]. Many asymmetric versions of these reactions have been developed so far [74]. Among the latter, the first catalytic enantioselective Michael addition of thiols to acyclic α,β,γ,δ-unsaturated dienones occurring regioselectively at the δ-position was reported by White and Shaw, in 2015 [75]. The reaction was catalyzed in dichloroethane at 25 °C by 10 mol% of chiral salen iron complex **93** in the presence of AgBF₄ as an additive. As shown in Scheme 39, aliphatic and aromatic thiols **94** as well as thioacetic acid regioselectively added to variously substituted acyclic α,β,γ,δ-unsaturated dienones **95** to give the corresponding chiral *trans*-δ-thia-α,β-unsaturated ketones **96** in uniformly high yields (72–98%), diastereoselectivities (84–88% de) and enantioselectivities (82–96% ee).

Later, a related catalyst **97** was applied by the same authors to promote the asymmetric Michael addition of thiols **94** to acyclic α,β-unsaturated ketones **67** [76]. In this case, 20 mol% of catalyst loading was required to provide the corresponding chiral *syn*-β-thio ketones **98** in remarkable yields (89–98%), diastereo- and



R¹ = Ph, *o*-Tol, *m*-Tol, *p*-Tol, *p*-MeOC₆H₄, *p*-*t*-BuC₆H₄, *m*-MeOC₆H₄,
p-MeOC₆H₄, *p*-FC₆H₄, *m*-ClC₆H₄, *p*-ClC₆H₄, 2,3,4-Cl₃C₆H₂, *p*-BrC₆H₄,
p-NCC₆H₄, *p*-F₃CC₆H₄, *p*-O₂NC₆H₄, 2-Naph, 2-furyl, 2-thienyl, 3-thienyl,
n-nonyl, *c*-Pent, Cy, *t*-Bu, 1-adamantyl
R² = *t*-Bu, Et, *i*-Pr, *o*-Pent, Cy, 1-adamantyl

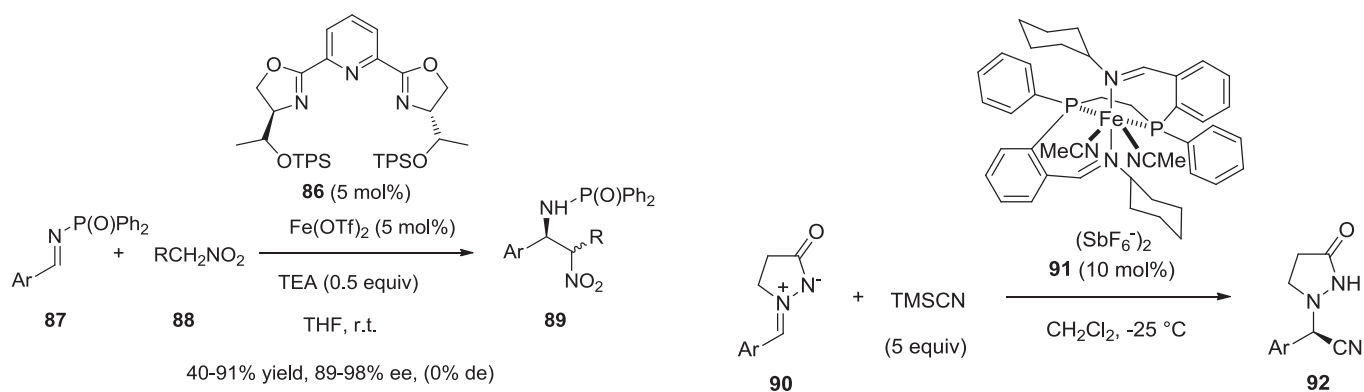
Scheme 35. Intramolecular Cannizzaro reaction [69].



73-91% yield, 41-82% ee

R = Ph, *p*-MeOC₆H₄, *m*-MeOC₆H₄, *o*-MeOC₆H₄, *p*-Tol, *m*-Tol, *p*-Me₂NC₆H₄,
2,3,4-MeO₃C₆H₂, *p*-FC₆H₄, *p*-BrC₆H₄, *m*-ClC₆H₄, 2-thienyl, 2-(5-methyl)-thienyl,
(*E*)-PhCH=CH, (*E*)-PhCH=C(Me), 1-Naph, Bn(CH₂)₂

Scheme 36. Hydrophosphonylation of aldehydes [70].

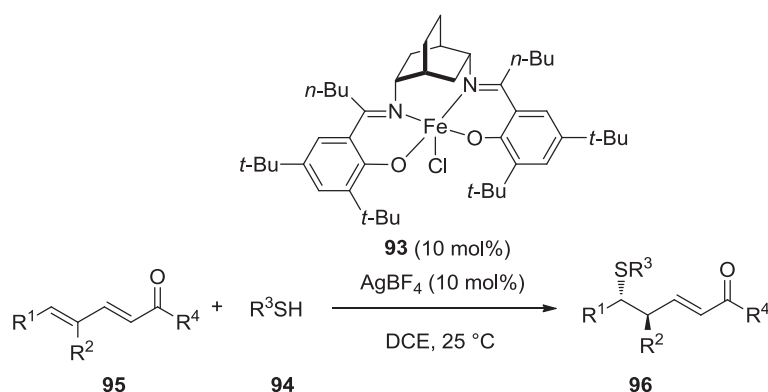


Ar = Ph, *p*-Tol, *p*-MeOC₆H₄, *p*-ClC₆H₄, *p*-F₃CNC₆H₄, *p*-O₂NC₆H₄,
m-O₂NC₆H₄, *o*-O₂NC₆H₄, 2-furyl, 2-Naph, (*E*)-PhCH=CH
R = H, Me, CH₂OTBS

Scheme 37. Nitro-Mannich reaction [71].

Ar = Ph, *p*-MeOC₆H₄, *p*-F₃CNC₆H₄

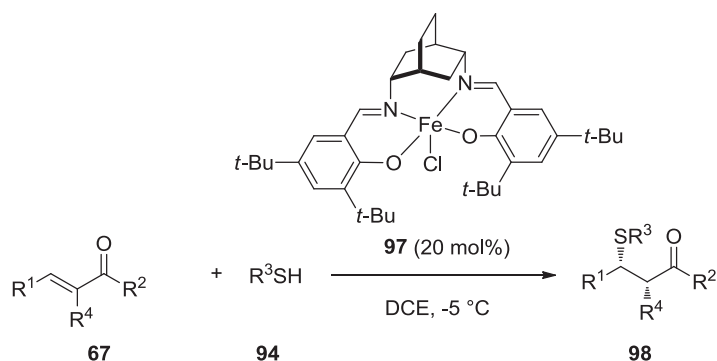
Scheme 38. Strecker reaction [72].



72-98% yield, 84-88% de, 82-96% ee

R¹ = Ph, Me
R² = H, Me, Br
R³ = Bn, Et, *t*-Bu, Ph, Ac
R⁴ = Me, Ph, *o*-MeOC₆H₄, 3,4-(MeO)₂C₆H₃, 2-furyl, 2-thienyl, OEt

Scheme 39. Michael addition of thiols to acyclic α,β,γ,δ-unsaturated dienones [75].



89–98% yield, >92–>96% de, 92–98% ee

R^1 = Ph, *m*-MeOC₆H₄, *p*-MeOC₆H₄, *p*-F₃CC₆H₄, *p*-ClC₆H₄, 2,6-Cl₂C₆H₃, 2,4-(O₂N)₂C₆H₃, 4-HO-3-MeOC₆H₃, 1-Naph, Me, *n*-Hex, *i*-Pr, Cy
 R^2 = Ph, Me, 2-furyl, 2-thienyl
 R^3 = Bn, Et, *i*-Pr, *t*-Bu, *p*-ClC₆H₄, (CH₂)₂OH, *n*-Bu, Ph
 R^4 = H, Me, Bu

Scheme 40. Michael addition of thiols to acyclic α,β -unsaturated ketones [76].

enantioselectivities (>92–>96% de and 92–98% ee, respectively), as shown in Scheme 40.

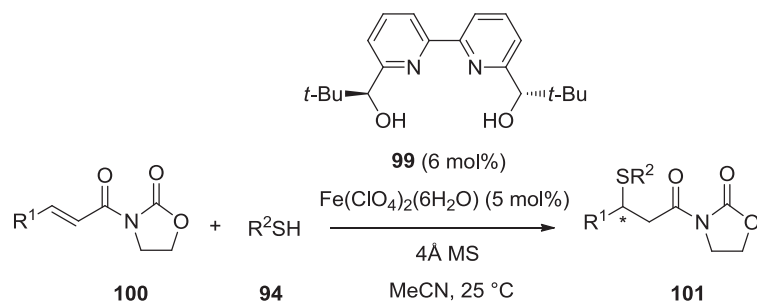
In 2017, Ollevier and Gandon developed enantioselective Michael additions of thiols to α,β -unsaturated oxazolidin-2-ones catalyzed by a chiral iron catalyst [77]. The latter was in situ generated from 5 mol% of Fe(ClO₄)₂(6H₂O) and 6 mol% of chiral bipyridine ligand **99** in acetonitrile at 25 °C. As shown in Scheme 41, the asymmetric sulfa-Michael addition of a wide variety of aliphatic and (hetero)aromatic thiols **94** to various (*E*)- α,β -unsaturated oxazolidin-2-ones **100** provided the corresponding chiral highly functionalized products **101** in good to quantitative yields (66–98%) and generally high enantioselectivities of up to 92% ee.

7. Enantioselective cross-coupling reactions

Over the past decades, transition metal-catalyzed cross-coupling reactions have become very efficient transformations for the elaboration of carbon–carbon and carbon–heteroatom bonds [78]. Iron catalysts have been introduced to promote these

challenging reactions only recently [79]. As an example, Pappo et al. reported enantioselective iron-catalyzed oxidative homo- and cross-couplings of 2-naphthols **102**, in 2016 [80]. The process was catalyzed by 2.5 mol% of novel iron phosphate complex **103** bearing chiral phosphoric acid ligands derived from BINOL. As shown in Scheme 42, it allowed for the first time the synthesis of C₁- and C₂-symmetric BINOLs **104** in which the 3 and 3' positions were available for further chemical transformations. These chiral products were generated at room temperature in the presence of *t*-BuOO*t*-Bu as an oxidant with moderate to excellent yields (33–94%) and enantioselectivities (54–92% ee).

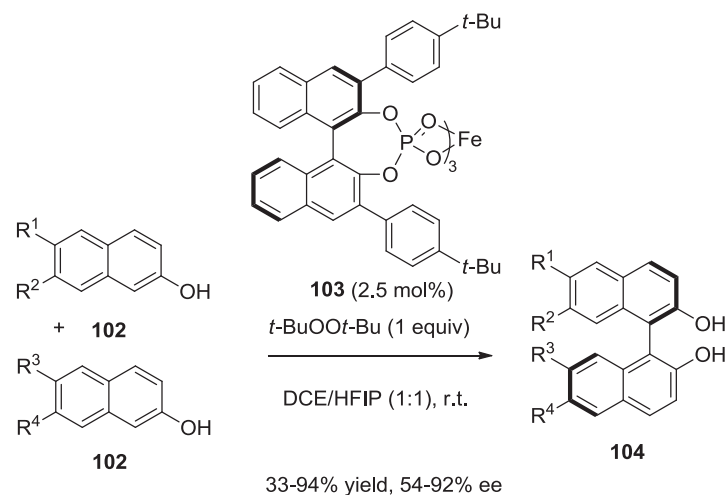
In 2017, these reactions were also investigated by Bryliakov et al. by using atmospheric oxygen as a green oxidant and chiral bipyridine-derived aminopyridine dinuclear iron complex **105** [81]. As shown in Scheme 43, in this case the aerobic processes were performed with only 1 mol% of catalyst **105** in chlorobenzene at 50 °C, providing the corresponding chiral BINOLs **104** in comparable yields (36–93%) albeit with lower enantioselectivities (13–56% ee).



66–98% yield, 6–92% ee

R^1 = Me, Ph, CO₂Et, CF₃
 R^2 = *p*-*t*-BuC₆H₄, *p*-Tol, *p*-MeOC₆H₄, *p*-ClC₆H₄, *o*-ClC₆H₄, Ph, *o*-Tol, pyridyl, 2-furyl, *n*-Bu, *i*-Pr, Bn

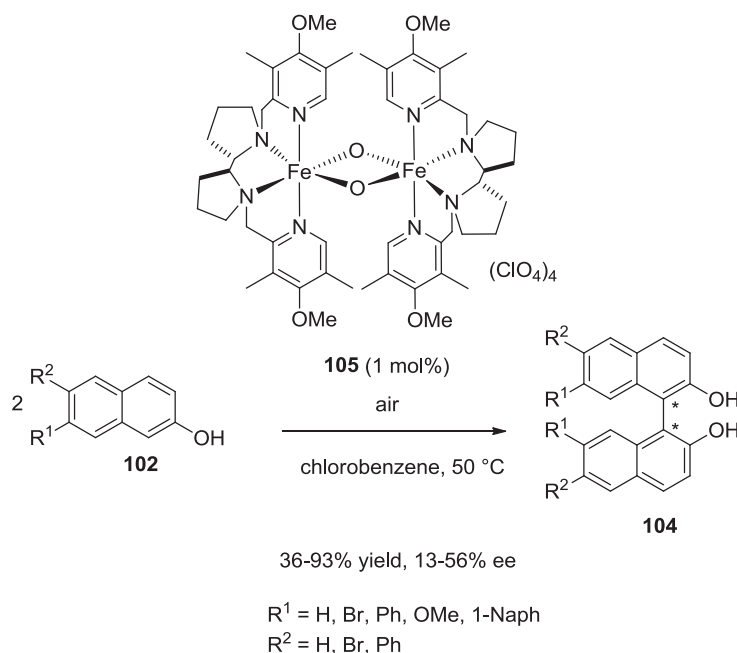
Scheme 41. Michael addition of thiols to α,β -unsaturated oxazolidin-2-ones [77].



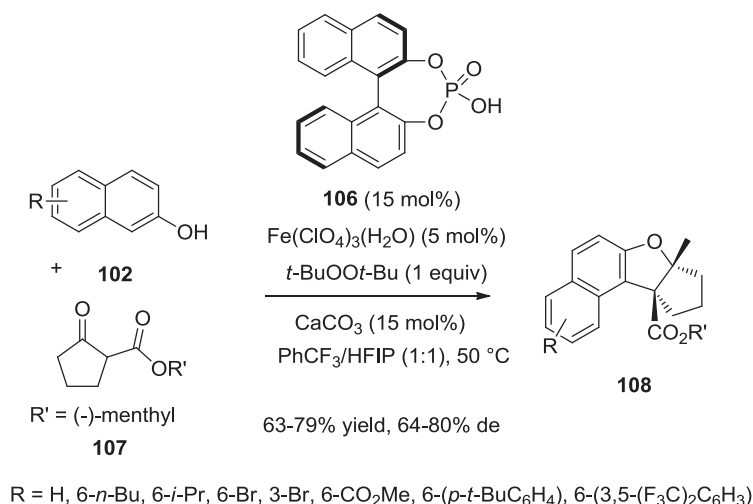
Scheme 42. Oxidative homo- and cross-couplings of 2-naphthols with *t*-BuOO*t*-Bu as an oxidant [80].

In 2017, Pappo and Narute reported the use of an iron phosphate catalyst in situ generated from 5 mol% of $Fe(ClO_4)_3(H_2O)$ and 15 mol% of chiral phosphoric acid **106** to promote the enantioselective cross-dehydrogenative coupling of 2-naphthols **102** with a chiral β -ketoester derived from (–)-menthol **107** [82]. Actually, the reaction occurred through double induction, leading to a variety of chiral polycyclic hemiacetals **108** in good to high yields (63–79%) and diastereoselectivities (64–80% de), as shown in Scheme 44. The catalyst system was found efficient for a variety of 2-naphthol derivatives bearing substituents at the 6- and 3-positions.

In another area, Nakamura et al. recently reported the first iron-catalyzed enantioselective cross-coupling reaction between an organometallic compound and an organic electrophile [83]. Indeed, the asymmetric cross-coupling reaction of aryl Grignard reagents **109** with α -chloroesters **110** was achieved in tetrahydrofuran at 0 °C in the presence of 3 mol% of $Fe(acac)_3$ and 6 mol% of chiral biphosphine ligand **111** to give the corresponding chiral α -arylalkanoic acid derivatives **112** in low to high yields (25–92%) and enantioselectivities (16–82% ee), as shown in Scheme 45. Moreover, asymmetric cross-couplings between aryl Grignard reagents and secondary alkyl halides catalyzed by chiral iron



Scheme 43. Aerobic coupling of 2-naphthols [81].



Scheme 44. Cross-dehydrogenative coupling of 2-naphthols with β -ketoesters [82].

bisoxazolinyphenylamido pincer complexes were developed by Hu et al., providing low enantioselectivities ($\leq 19\%$ ee) [84].

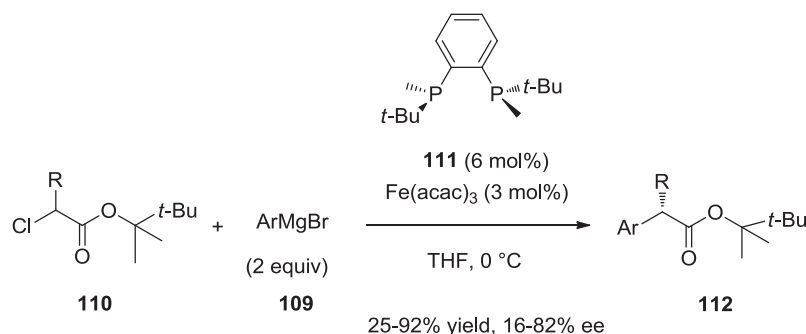
In 2017, the asymmetric aerobic oxidative cross-coupling of tetrahydroisoquinolines with alkynes was reported by Feng and Liu on the basis of a chiral *N,N'*-dioxide ligand **113**/zinc(II)/iron (II) bimetallic cooperative catalytic system [85]. As shown in Scheme 46, this catalyst system proved to be efficient for the formation of various chiral α -alkynyl substituted tetrahydroisoquinolines **114** starting from the corresponding tetrahydroisoquinolines **115** and alkynes **116**. The products were formed with low to high yields (22–82%) and moderate to excellent enantioselectivities (37–99% ee) in dichloroethane at 35 °C in the presence of oxygen as the sole oxidant.

8. Enantioselective cyclizations

The cyclopropanation of alkenes [44b,86] based on the transition-metal-catalyzed decomposition of diazoalkanes has been widely developed [87]. Among various metal catalysts employed in these reactions are chiral iron complexes. As recently reported excellent results, the first enantioselective intramolecular

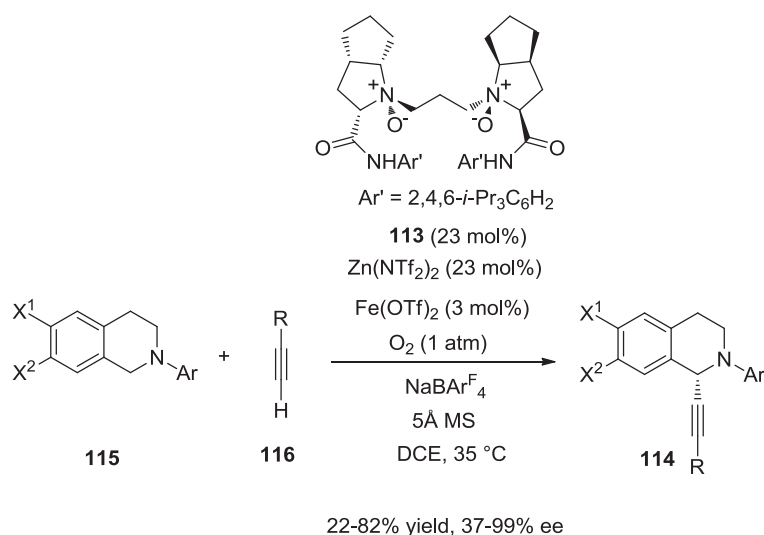
cyclopropanation of indoles was developed by Zhou and Zhu, in 2017 [88]. It employed a chiral iron catalyst in situ generated from 10 mol% of $\text{Fe}(\text{ClO}_4)_2$ and 12 mol% of chiral spiro bisoxazoline ligand **117** in chloroform. As shown in Scheme 47, the reaction of a range of aromatic diazo compounds **118** afforded at 60 °C the corresponding chiral polycyclic products **119** bearing three contiguous stereogenic centers in moderate to high yields (52–90%) and remarkable enantioselectivities (95–>99% ee). On the other hand, moderate enantioselectivities ($\leq 53\%$ ee) were reported by Roelfes et al. in the asymmetric cyclopropanation of styrenes with ethyl diazo acetate catalyzed by a novel DNA-based hybrid catalyst comprised of salmon testes DNA and an iron(III) complex of a cationic *meso*-tetrakis(*N*-alkylpyridyl)porphyrin [89].

In 2018, Ollevier et al. demonstrated that a chiral iron catalyst, in situ generated from $\text{Fe}(\text{ClO}_4)_2$ and chiral bipyridine diol ligand *ent*-**99** in acetonitrile, was able to promote highly enantioselectively the Diels-Alder cycloaddition of 3-acryloyloxazolidinones **100** with cyclic dienes **120** [90]. For example, the reaction of cyclopentadiene (*n* = 1) with various 3-acryloyloxazolidinones **100** afforded the corresponding chiral *endo*-cycloadducts **121** in high yields (70–95%), moderate to high diastereoselectivities (48–88% de) and low to excellent enantioselectivities (12–98%



Ar = Ph, *p*-PhC₆H₄, *p*-*i*-BuC₆H₄, 2-(*p*-MeO)Naph, *p*-(Me₂N)C₆H₄, *p*-MeOC₆H₄, *m*-MeOC₆H₄, *p*-Tol, *m*-Tol, *o*-Tol, 3,5-Me₂C₆H₃, *p*-(allylCH₂)C₆H₄, 2-Naph, 1-Naph, *p*-FC₆H₄, 3,4-F₂C₆H₃, 3,5-F₂C₆H₃, 3,4,5-F₃C₆H₂, 3-Cl-4-FC₆H₃, 3,4-Cl₂C₆H₃,
 R = Me, *i*-Bu, Et, CH₂OMe

Scheme 45. Cross-coupling of α -chloroesters with aryl Grignard reagents [83].



$\text{R} = \text{Ph}, p\text{-ClC}_6\text{H}_4, p\text{-BrC}_6\text{H}_4, p\text{-Tol}, p\text{-EtC}_6\text{H}_4, p\text{-PrC}_6\text{H}_4, p\text{-BuC}_6\text{H}_4, p\text{-PentC}_6\text{H}_4, p\text{-MeOC}_6\text{H}_4, p\text{-MeO}_2\text{CC}_6\text{H}_4, p\text{-NCC}_6\text{H}_4, o\text{-ClC}_6\text{H}_4, m\text{-FC}_6\text{H}_4, m\text{-ClC}_6\text{H}_4, m\text{-Tol}, m\text{-MeOC}_6\text{H}_4, m\text{-O}_2\text{NC}_6\text{H}_4, 3,5\text{-F}_2\text{C}_6\text{H}_3, 1\text{-Naph}, 2\text{-thienyl}, \text{CH}_2\text{Bn}, c\text{-Pr}$
 $\text{X}^1 = \text{H}, \text{OMe}$
 $\text{X}^2 = \text{H}, \text{OMe}$
 $\text{X}^1, \text{X}^2 = \text{OCH}_2\text{O}$

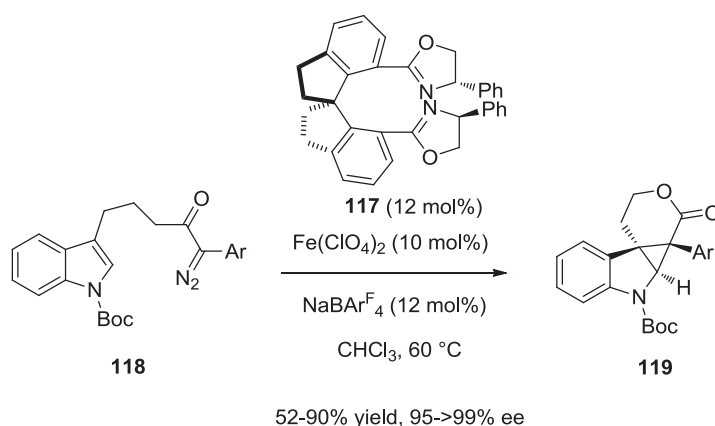
Scheme 46. Oxidative cross-coupling of tetrahydroisoquinolines with alkynes [85].

ee) by using low catalyst loadings (2.4–4.8 mol%), as shown in Scheme 48. Acyclic dienes **122** were also compatible since they provided by reaction with unsubstituted 3-acryloyloxazolidinones **100** the corresponding chiral cyclohexenes **123** in comparable yields (60–80%) and slightly lower enantioselectivities (50–88% ee).

In another area, Lu et al. recently developed the first example of an iron-catalyzed asymmetric reductive cyclization of a 1,6-enyne such as **124** [91]. As shown in Scheme 49, the reaction performed in the presence of ZnEt_2 as a reducing agent was catalyzed at room temperature by iron complex **125** bearing a chiral oxazoline iminopyridine ligand, leading to the corresponding chiral pyrrolidine **126** in 66% yield and 39% ee.

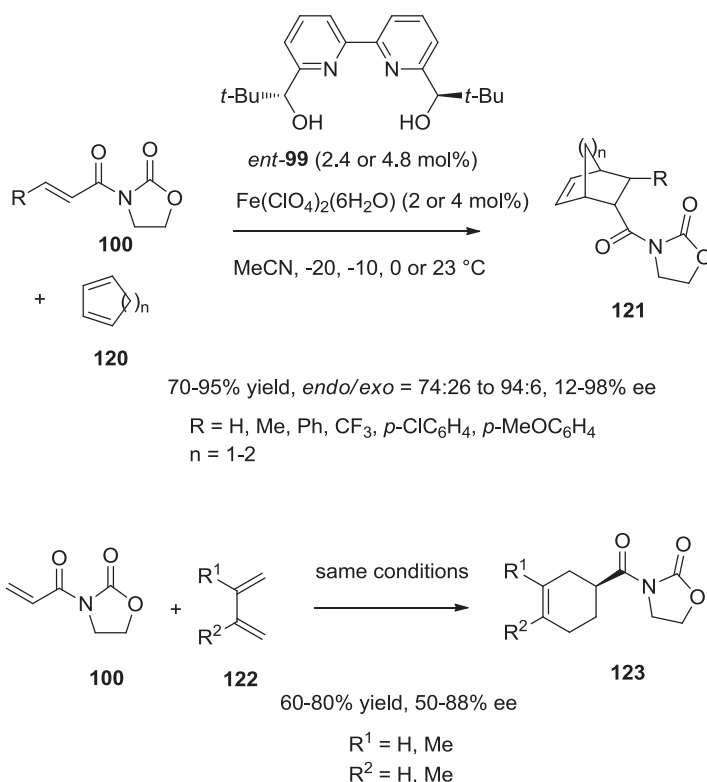
In 2016, Katsuki and Uchida reported iron-catalyzed asymmetric aerobic dearomatizing spirocyclization of unsymmetrical methylenebis(arenol)s [92]. The process was performed in toluene at 90 °C using atmospheric oxygen as a simple oxidant. Catalyzed by 8 mol% of chiral salan iron catalyst **127**, the oxidative spirocyclization of various functionalized methylenebis(arenol)s **128** afforded the corresponding chiral spirocyclic ketones **129** in uniformly good to high yields (66–89%) and enantioselectivities (77–87% ee), as shown in Scheme 50.

In addition, White and Shaw reported the use of 7.5 mol% of chiral salen iron complex **130** in chloroform at 50 °C to promote the asymmetric Conia-ene carbocyclization of a range of alkynyl ketones **131** bearing an electron-withdrawing α -substituent (R^2)



$\text{Ar} = \text{Ph}, p\text{-BrC}_6\text{H}_4, p\text{-F}_3\text{CC}_6\text{H}_4, m\text{-BrC}_6\text{H}_4, m\text{-MeOC}_6\text{H}_4, o\text{-ClC}_6\text{H}_4, o\text{-BrC}_6\text{H}_4$

Scheme 47. Intramolecular cyclopropanation of indoles [88].



Scheme 48. Diels-Alder reactions of 3-acryloyloxazolidinones with dienes [90].

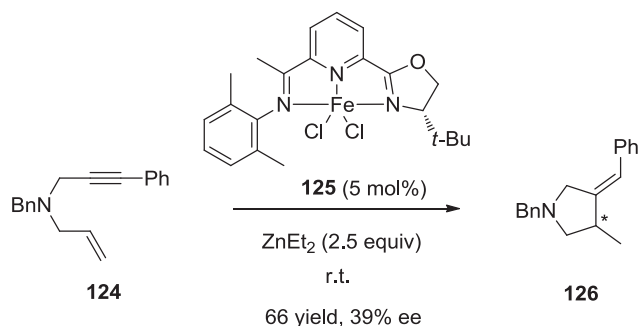
[76]. The resulting chiral *exo*-methylenecyclopentanes **132** exhibiting a quaternary stereogenic center were obtained in both excellent yields (80–98%) and enantioselectivities (90–98% ee), as shown in Scheme 51.

9. Enantioselective ring-openings of epoxides

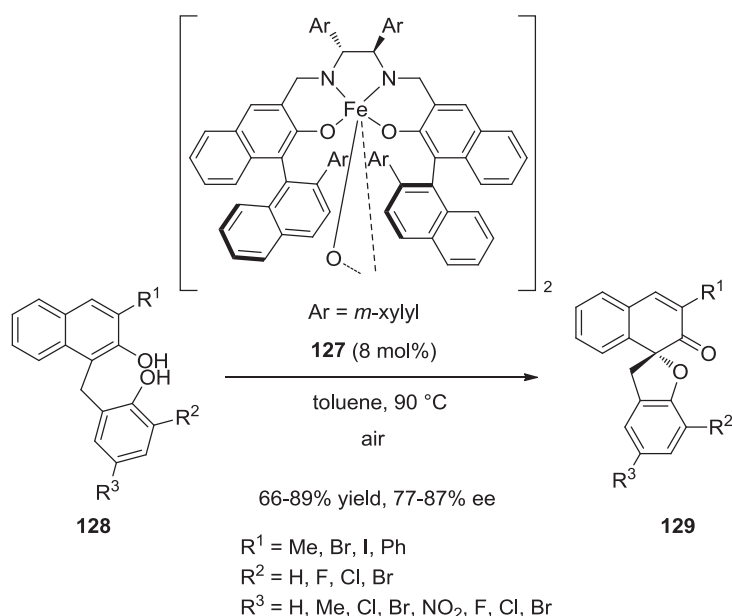
The desymmetrization of *meso*-epoxides with anilines represents a simple strategy for the synthesis of pivotal chiral β -amino alcohols. In this context, Kureshy et al. recently synthesized novel recyclable efficient dinuclear chiral iron complexes to promote the asymmetric ring-opening of *meso*-stilbene oxide **133** with anilines **134** [93]. The active catalyst was in situ generated in dichloromethane at room temperature from 5 mol% of Fe(acac)₃ and 2.5 mol% of chiral tridentate ligand **135**. The corresponding chiral β -amino alcohols **136** were obtained in low to quantitative yields

(20–95%) and moderate to excellent enantioselectivities (38–99% ee), as shown in Scheme 52. Interestingly, it was found that the catalyst was easily recovered and reused up to five times.

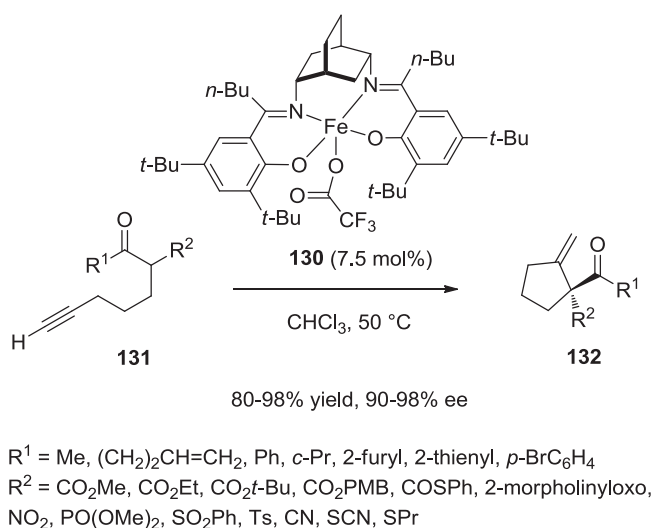
In the same year, related reactions were also investigated by Islam and Bhaumik by using a novel mesoporous SBA-15-supported iron catalyst **Fe@SBAL** [94]. As shown in Scheme 53, the ring-opening of cyclohexene epoxide **137** with anilines **134** performed at room temperature under solvent-free conditions in the presence of only 0.4 mol% of this grafted mesoporous catalyst allowed the corresponding chiral β -amino alcohols **138** to be achieved in excellent yields (85–96%) and remarkable enantioselectivities (>96–99% ee). Similar reaction conditions were also compatible to the ring-opening of terminal racemic epoxides **139** with aniline **134a**, as shown in Scheme 53. Styrene oxide **139a** (R = Ph) underwent cleavage by aniline **134a** through a regioselective manner with a preferential attack at the benzylic carbon atom to give the corresponding (*S*)- β -amino alcohol **141a** with both excellent enantioselectivity (96% ee) and yield (97%). Surprisingly, except styrene oxide, all other terminal epoxides **139** provided regioselectively the corresponding (*R*)- β -amino alcohol **140** with excellent enantioselectivities (83–>99% ee) and yields (85–98%). In spite of these excellent results, the lack of recyclability of catalyst **Fe@SBAL** represented a major drawback. To address this issue, the authors developed another related functionalized mesoporous SBA-15 catalyst grafted with an iron complex derived from a chiral amino alcohol (**Fe@SBEP**) which was recyclable up to five times without loss of both activity and enantioselectivity in similar reactions [95]. By using 0.5 mol% of this mesoporous catalyst at room temperature under solvent free conditions, the chiral β -amino alcohols arisen from the ring-openings of cyclohexene oxide and various racemic terminal epoxides with anilines were obtained in high to quantitative yields (86–98%) and good to excellent enantioselectivities (72–>99% ee).



Scheme 49. Reductive cyclization of a 1,6-enyne [91].



Scheme 50. Aerobic dearomatizing spirocyclization of unsymmetrical methylenebis(arenol)s [92].



Scheme 51. Conia-ene reaction of alkynyl ketones [76].

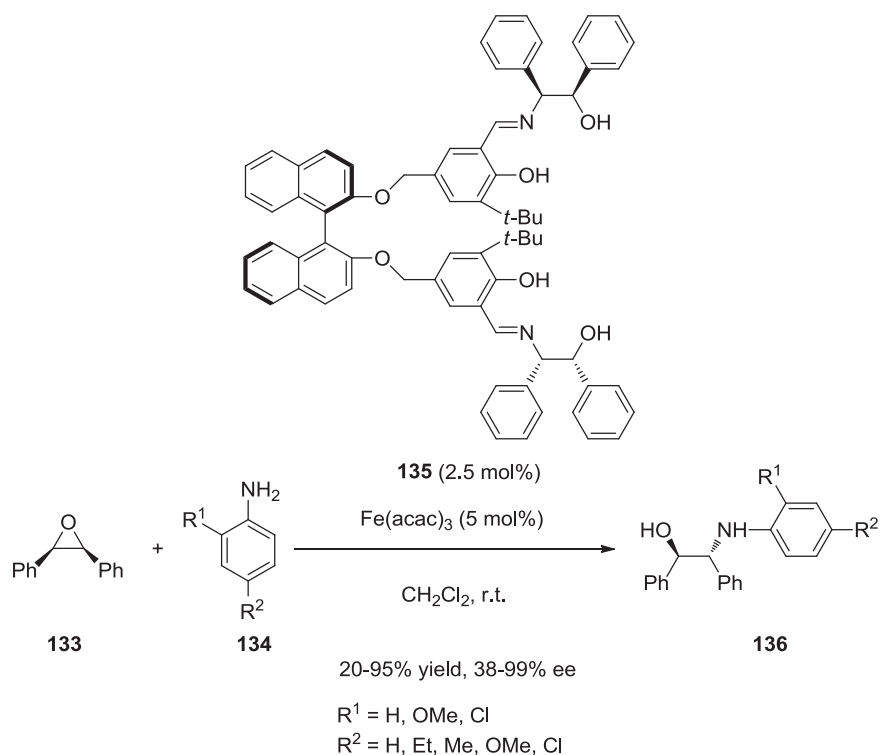
10. Enantioselective domino reactions

One-pot domino reactions [96] have allowed the synthesis of many complex natural and/or biologically active products [97], avoiding costly and time-consuming protection-deprotection processes, as well as purification procedures of intermediates [98]. So far, only few asymmetric versions of these reactions mediated by chiral iron catalysts have been described. As a recent example, Punniyamurthy et al. developed in 2018 enantioselective iron-catalyzed domino sulfa-Michael/aldol reactions between aromatic α,β -unsaturated ketones **44** and 1,4-dithiane-2,5-diol **142** [99]. This new methodology employed as a catalyst system a combination of 15 mol% of FeCl_3 and 5 mol% of a novel chiral dendrimer ligand **143** in a 2:1 mixture of toluene and dichloroethane as a solvent. It afforded a series of chiral tetrahydrothiophenes **144** as sin-

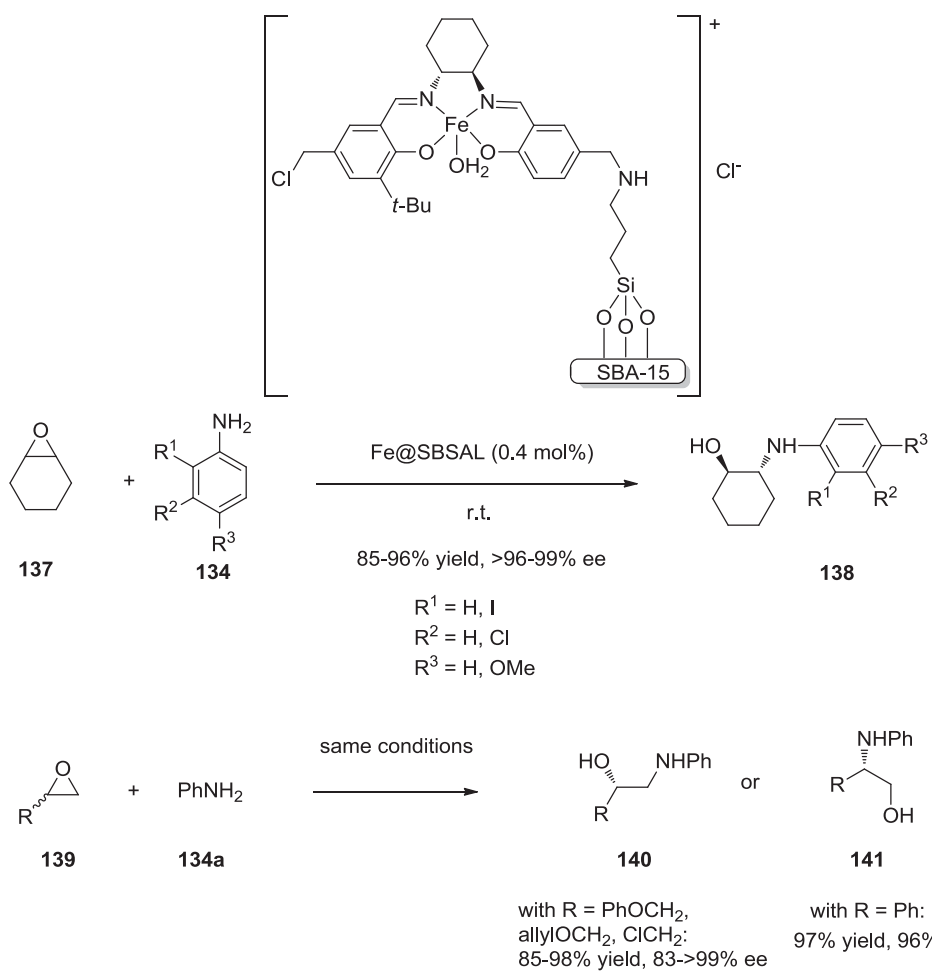
gle diastereomers in low to high yields (21–84%) and low to moderate enantioselectivities (16–70% ee), as shown in Scheme 54. The chiral dendritic catalyst was easily recovered and reused for three runs without loss of activity and selectivity. This work represented the first example of a metal-catalyzed domino sulfa-Michael/aldol reaction between chalcones and 1,4-dithiane-2,5-diol.

In another context, achiral iron complexes can be used in combination with chiral organocatalysts to promote multicatalyzed domino reactions [100]. For example, Quintard and Rodriguez recently combined achiral iron tricarbonyl complex **145** (6.5 mol%) with chiral proline-derived organocatalyst **146** (8 mol%) in the presence of $\text{Cu}(\text{acac})_2$ (5 mol%) as an additive to promote enantioselective domino oxidation/Michael/reduction/Claisen fragmentation reactions of 1,3-diketones **147** with allylic alcohols **148** (Scheme 55) [101]. The multicatalyst system employed at 25 °C in xylenes allowed the corresponding chiral 3-alkylpentanols **149** to be achieved in good yields (66–85%) and uniformly high enantioselectivities (87–96% ee). The mechanism of the domino reaction is depicted in Scheme 55. It began with the iron-catalyzed oxidation of the allylic alcohol **148** into α,β -unsaturated aldehyde **A** which subsequently underwent a Michael addition with the 1,3-diketone **147** through iminium catalysis from chiral organocatalyst **146** to afford intermediate **B**. A chemoselective aldehyde reduction of the latter led to alcohol intermediate **C** that further cyclized into lactol **D**. Then, intermediate **D** was submitted to a Claisen fragmentation to give intermediate **E** which led after protonation to the final chiral product **149**.

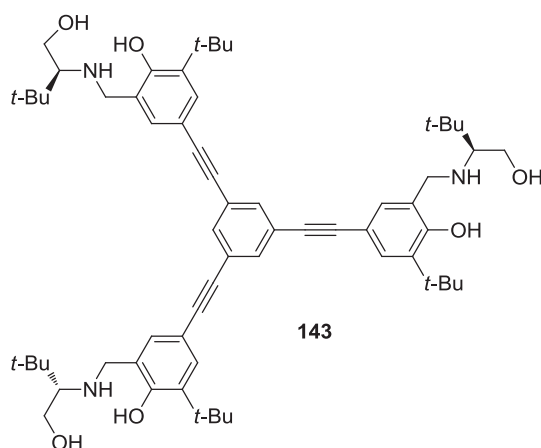
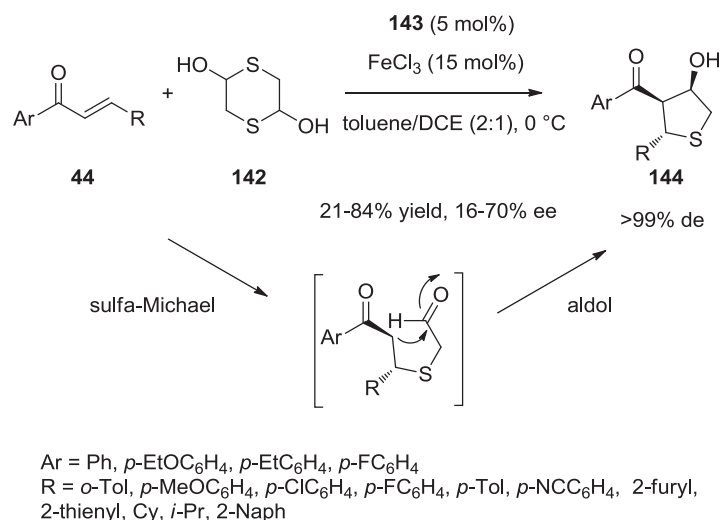
In 2018, the same authors applied a related multicatalyst system to develop another type of enantioselective domino reactions [102]. Indeed, the use of a multicatalytic system composed of 6.5 mol% of achiral iron tricarbonyl complex **145**, 13 mol% of chiral proline-derived organocatalyst **150** and 5 mol% of $\text{Cu}(\text{acac})_2$ allowed enantioselective domino oxidation/Michael/reduction reactions between cyclic β -keto esters **151** and allylic alcohols **148** to occur in xylenes at 10 °C (Scheme 56). The domino products **152** were subsequently submitted to lactonization by treatment with DBU at room temperature in toluene to give the correspond-



Scheme 52. Ring-opening of *meso*-stilbene oxide with anilines [93].



Scheme 53. Ring-openings of various epoxides with anilines catalyzed by a mesoporous SBA-15-supported iron catalyst [94].



Scheme 54. Domino sulfa-Michael/aldol reaction of aromatic α,β -unsaturated ketones with 1,4-dithiane-2,5-diol [99].

ing chiral δ -lactones **153** in low to moderate yields (21–51%) combined with high enantioselectivities (90–93% ee).

11. Miscellaneous enantioselective reactions

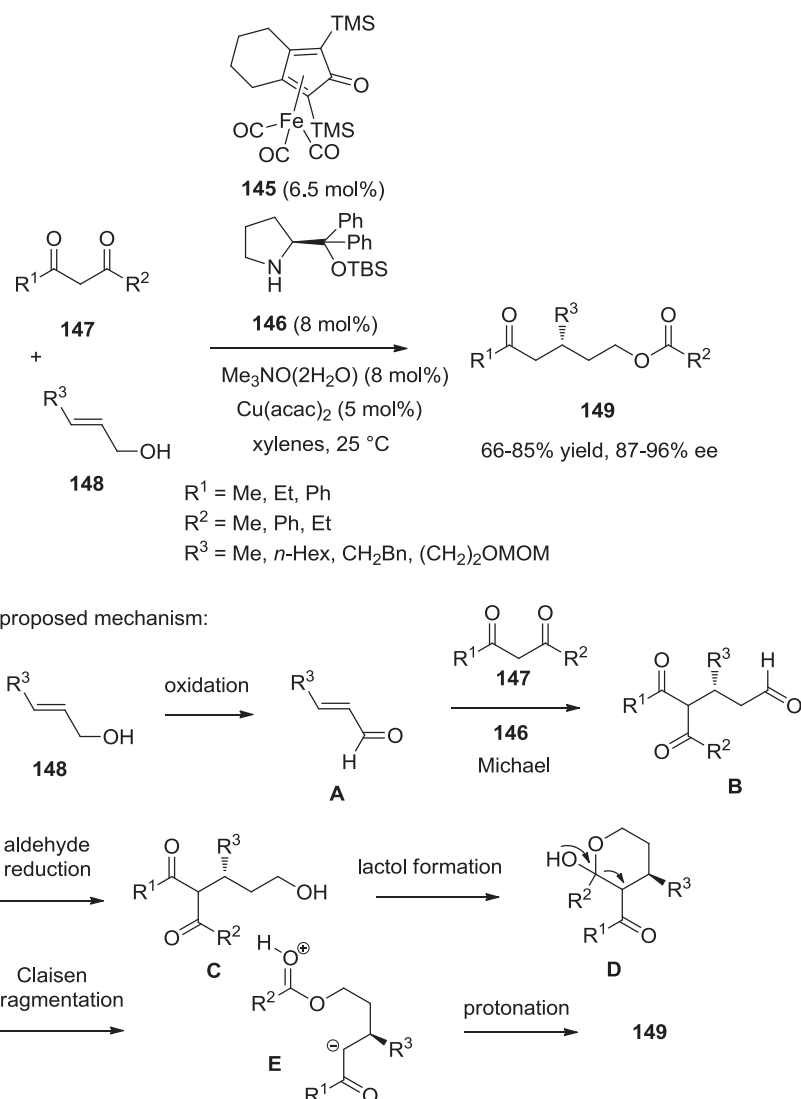
Among other types of enantioselective reactions catalyzed by chiral iron complexes are asymmetric oxidations of alkyl aryl sulfides which were reported by Ollevier et al., in 2017 [103]. These simple processes performed in tetrahydrofuran at $-25\text{ }^{\circ}\text{C}$ were catalyzed by an iron complex in situ generated from 8 mol% of FeCl_2 and 10 mol% of chiral bis(oxazoliny)bipyridine ligand **154**, as depicted in Scheme 57. Under these mild reaction conditions, the oxidation of a range of alkyl aryl sulfides **155** with aqueous H_2O_2 led to the corresponding chiral sulfoxides **156** in low to good yields (21–61%) and moderate to excellent enantioselectivities (36–96% ee). Notably, the chiral ligand could be easily recycled at the end of the reaction.

The potential of enantioselective iron catalysis in drug manufacturing on a large scale was demonstrated in 2018 by Nishiguchi et al., who reported a kilogram scale synthesis of a proton pump inhibitor esomeprazole based on an asymmetric iron-catalyzed sulfoxidation [104]. As depicted in Scheme 58, prochiral sulfide

157 was oxidized by treatment with H_2O_2 in acetonitrile as a solvent in the presence of 4-dimethylaminobenzoic acid and lithium carboxylate as additives to give esomeprazole in both excellent yield (88%) and enantioselectivity (>99% ee). The process was performed at -15 to $-6\text{ }^{\circ}\text{C}$ on a 4.66 kg scale by using a chiral iron catalyst in situ generated from 8 mol% of $\text{Fe}(\text{acac})_3$ and 9 mol% of chiral Schiff base **158**.

In 2017, Ackermann et al. developed the first enantioselective iron-catalyzed C–H alkylations evolving through organometallic C–H activation [105]. Indeed, in the presence of a chiral catalyst in situ generated from 10 mol% of $\text{Fe}(\text{acac})_3$ and 20 mol% of novel designed chiral *meta*-1-adamantyl-derived N-heterocyclic carbene ligand **159**, the asymmetric C–H alkylation of indoles **160** with aromatic alkenes **161** was achieved in tetrahydrofuran at $45\text{ }^{\circ}\text{C}$ to provide the corresponding chiral carbaldehydes **162** in moderate to quantitative yields (41–98%) and moderate to high enantioselectivities (56–88% ee), as shown in Scheme 59. The catalyst system was compatible with a wide variety of substrates. The authors demonstrated the crucial importance of remote *meta*-substitution on the NHC ligand to achieve both high stereoselectivity and yield.

In another area, Che et al. reported the use of a novel chiral bipyrrrolidine salan iron complex **163** to promote asymmetric chlo-



Scheme 55. Multicatalytic domino oxidation/Michael/reduction/Claisen fragmentation reaction of 1,3-diketones with allylic alcohols [101].

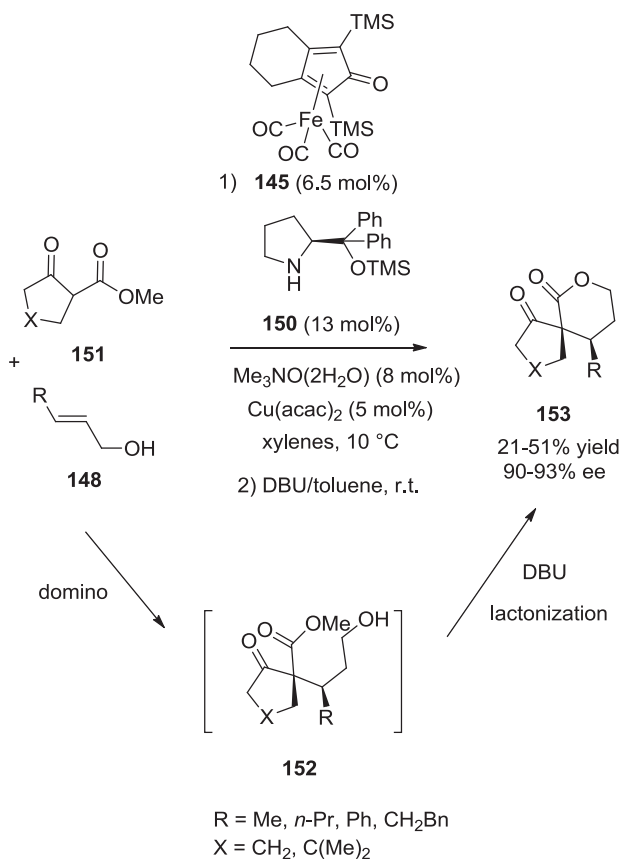
rinations of β -keto esters with *N*-chlorosuccinimide (NCS) as a chlorination agent [106]. The reactions of a range of cyclic β -keto esters **164** with NCS were catalyzed by 5 mol% of this iron complex in dichloromethane at -20°C in the presence of 5 mol% of AgClO_4 , thus providing the corresponding chiral chlorinated products **165** in uniformly high yields (81–99%) and moderate to high enantioselectivities (48–92% ee). The scope of the reaction was extended to the asymmetric chlorination of *N*-Boc oxindoles **166** into products **167** with moderate to high yields (29–99%) and enantioselectivities (47–91% ee), as shown in Scheme 60.

In 2017, a general and efficient methodology to synthesize chiral arylpyrroles was reported by Tan et al. on the basis of the first catalytic asymmetric Paal–Knorr reaction [107]. This reaction occurred at 0°C between 1,4-diones **168** and anilines **134** in a mixture of tetrachloromethane and cyclohexane as a solvent in the presence of 10 mol% of $\text{Fe}(\text{OTf})_3$ and the same quantity of chiral phosphoric acid **169**. The use of this catalyst system allowed a wide range of axially chiral arylpyrroles **170** to be synthesized in both uniformly high yields (83–95%) and enantioselectivities (85–98% ee), as shown in Scheme 61.

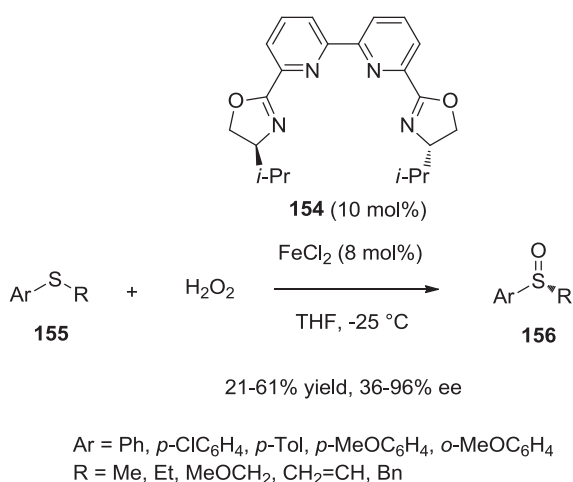
12. Conclusions

This review demonstrates that iron is today capable of covering almost the entire range of asymmetric organic synthesis. Indeed, a wide variety of enantioselective transformations have been developed in the presence of various types of novel chiral iron catalysts to replace complexes derived from more rare, expensive and often toxic precious metals. In particular within the past few years, a range of highly enantioselective iron-catalyzed reactions have been described, providing an enormous potential for future synthesis and demonstrating that this field is growing rapidly. This review updates the recent developments reported since the beginning of 2015 in the field of all types of enantioselective transformations promoted by chiral iron catalysts, illustrating the power of these green catalysts to promote all types of highly enantioselective transformations with remarkable diversification outcomes.

For example, the progress made in the reduction of ketones is remarkable, especially in asymmetric transfer hydrogenations with enantioselectivities of up to 99% ee described by the groups of Mezzetti and Morris using respectively $(\text{NH}_2)_2\text{P}_2$ and PNHNP' chiral



Scheme 56. Multicatalytic domino oxidation/Michael/reduction reaction of cyclic β -keto esters with allylic alcohols followed by lactonization [102].



Scheme 57. Oxidation of alkyl aryl sulfides [103].

pincer ligands. Excellent enantioselectivities of up to 96% ee have also been recently reported in enantioselective hydrogenations of ketones by Morris using PNHP' chiral iron complexes and in that of benzoxazinones by Beller on the basis of relay iron/chiral phosphoric acid catalysis. Moreover, asymmetric hydrosilylations of ketones have been developed by Huang with up to 93% ee using iminopyridine-oxazoline chiral iron catalysts and by Gade with 99% ee by employing bis(oxazolinylmethylidene)isoindoline chiral iron complexes.

In another area, excellent results have been recently reported in asymmetric iron-catalyzed epoxidations of alkenes. For example, Costas obtained enantioselectivities of up to 92% ee in the epoxidation of cyclic α,β -unsaturated ketones and cyclohexene- and cyclopentene-1-ketones with H_2O_2 catalyzed by a chiral picoline-benzimidazole-bipyrrolidine iron complex. Even higher enantioselectivity levels (97% ee) were achieved by the same author in the epoxidation of α -substituted styrenes with H_2O_2 catalyzed by a chiral bipyrrolidine-derived aminopyridine iron complex in the presence of a chiral amino acid as a co-ligand. Moreover, Sun reported >99% ee for the epoxidation of aromatic α,β -unsaturated ketones catalyzed by a chiral aminopyridine-morpholine N4 iron complex. Oxidants other than H_2O_2 have also been employed, such as peracetic acid by Gao in the epoxidation of acyclic α,β -unsaturated aromatic ketones catalyzed by a chiral iron catalyst derived from a porphyrin-inspired ligand with 99% ee. Cui and Lui used PhIO as an oxidant in the epoxidation of chromenes catalyzed by a chiral heterogeneous iron complex derived from covalent organic framework with 92% ee.

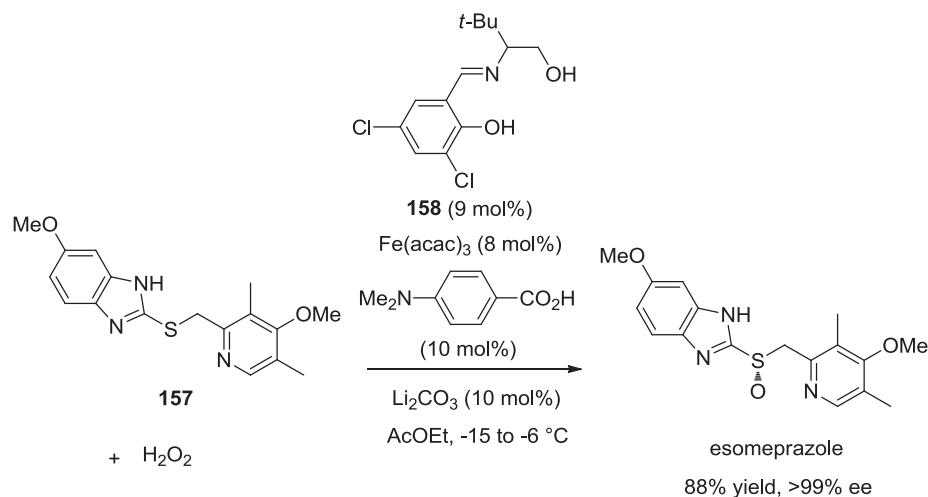
Various types of enantioselective iron-catalyzed additions to alkenes have been successfully developed, such as asymmetric diastereo- and enantioselective intramolecular aminochlorination of olefins reported by Xu based on the use of chiral bisoxazoline ligands that provided up to 92% ee. Feng employed *N,N'*-dioxide chiral ligands to promote enantioselective iron-catalyzed intramolecular haloetherifications of α,β -unsaturated ketones with 97% ee, bromoazidations of α,β -unsaturated ketones with >99% ee, and chloroazidation and iodoazidation of chalcone with 92–95% ee. On the other hand, highly enantioselective iron-catalyzed *cis*-dihydroxylations of alkenes using H_2O_2 as an oxidant have been developed by Che with tetradentate N4 chiral iron complexes with >99% ee. Other types of additions to alkenes have also been reported, such as the first highly regio- and enantioselective iron-catalyzed anti-Markovnikov hydrosilylation of 1,1-disubstituted aryl alkenes developed by Lu with >99% ee in the presence of a tridentate N3 chiral iron complex.

In the area of nucleophilic additions to carbonyl compounds and derivatives, excellent results have also been described. For example, enantioselectivities of up to 97% ee were reported for an asymmetric intramolecular Cannizzaro reaction of a range of aryl and alkyl glyoxal monohydrates performed with *N,N'*-dioxide chiral ligands. Comparable levels of enantioselectivity (98% ee) were also achieved by Mlynarski and Dudek in the first enantioselective addition of nitroalkanes to imines mediated by a chiral pybox iron catalyst.

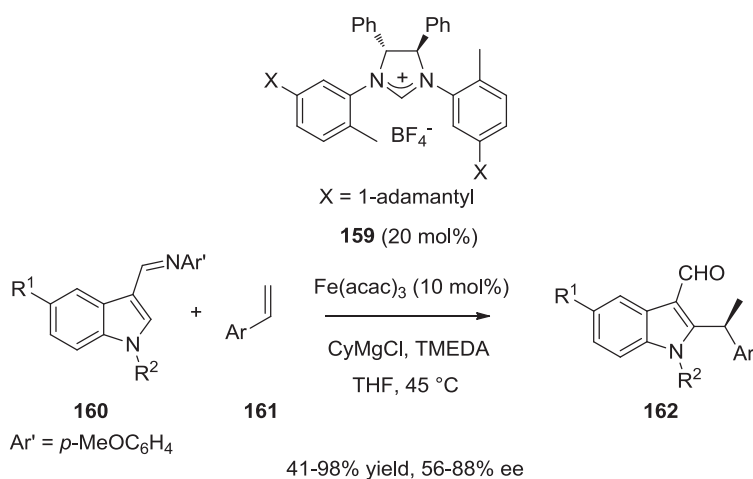
The sulfa-Michael reaction also encountered excellent results with enantioselectivities of 96% ee described by White and Shaw by using a chiral salen iron complex to promote the first catalytic enantioselective Michael addition of thiols to acyclic $\alpha,\beta,\gamma,\delta$ -unsaturated dienones occurring regioselectively at the δ -position. Even higher enantioselectivities (98% ee) were reached by these authors in the asymmetric Michael addition of thiols to acyclic α,β -unsaturated ketones using a related catalyst. In addition, Ollevier and Gandon developed enantioselective Michael additions of thiols to α,β -unsaturated oxazolidin-2-ones mediated by an iron complex derived from a chiral bipyridine ligand with 92% ee.

In the area of enantioselective coupling reactions, asymmetric oxidative homo- and cross-couplings of 2-naphthols reported by Pappo provided up to 92% ee by using a novel BINOL-derived chiral iron phosphate catalyst while even higher enantioselectivities of 99% ee were achieved by Feng and Liu in aerobic iron-catalyzed oxidative cross-coupling of tetrahydroisoquinolines with alkynes based on the use of a chiral *N,N'*-dioxide ligand.

Miscellaneous asymmetric cyclizations have also been based on asymmetric iron catalysis, such as the first enantioselective intramolecular cyclopropanation of indoles developed by Zhou



Scheme 58. Synthesis of esomeprazole through sulfoxidation [104].



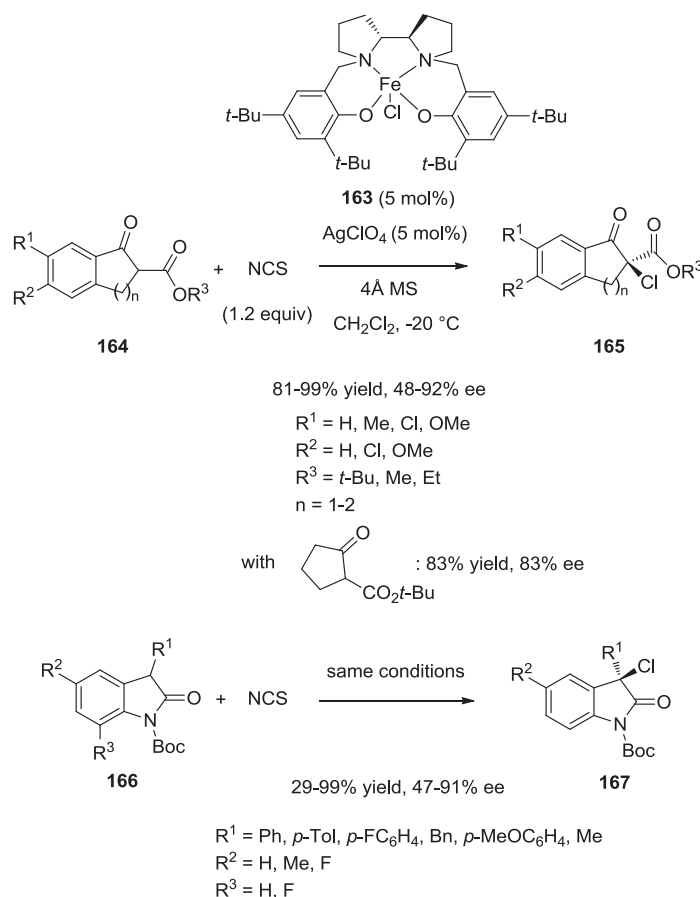
Scheme 59. C-H Alkylation of indoles with aromatic alkenes [105].

and Zhu in the presence of a chiral spiro bisoxazoline iron complex with enantioselectivities of up to >99% ee. Another iron complex derived from a chiral bipyridine diol ligand was successfully applied by Ollevier to promote highly enantioselectively the Diels-Alder cycloaddition of 3-acryloyloxazolidinones with dienes with 98% ee. Furthermore, White and Shaw have reported the use of chiral salen iron complexes to mediate the asymmetric Conia-ene carbocyclization of a range of alkynyl ketones with 98% ee.

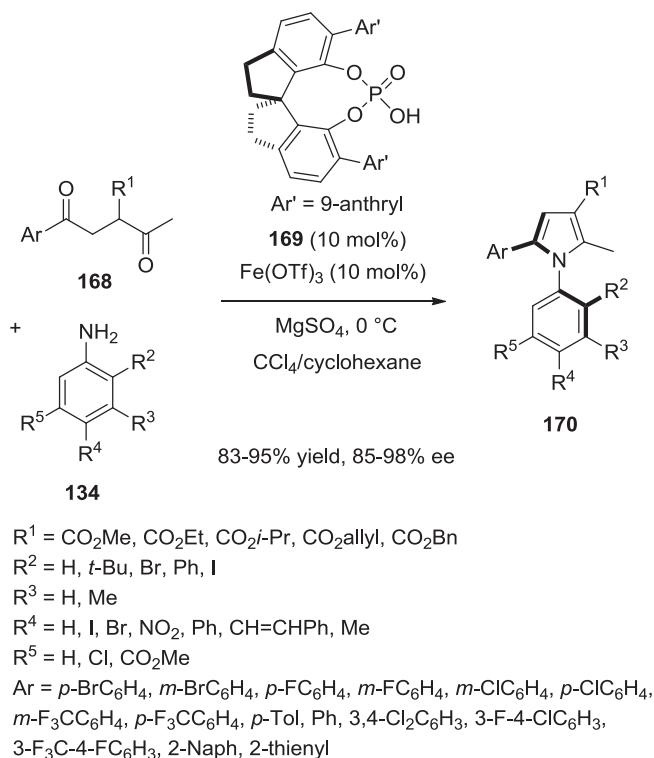
Chiral iron complexes are also able to catalyze the asymmetric ring-opening of various epoxides with remarkable enantioselectivities. For example, enantioselectivities of 99% ee were described by Kureshy in the ring-opening of *meso*-stilbene oxide with anilines

by using a chiral tridentate ligand but also by Islam and Bhaumik in ring-openings of various epoxides with anilines catalyzed by a mesoporous SBA-15-supported chiral iron catalyst.

Iron catalysts have also been involved in multicatalyzed enantioselective domino reactions. For example, Quintard and Rodriguez reported enantioselectivities of up to 96% ee in multicatalytic domino oxidation/Michael/reduction/Claisen fragmentation reactions of 1,3-diketones with allylic alcohols. The same authors also applied a related multicatalyst system based on the combination of an achiral iron tricarbonyl complex, a chiral proline-derived organocatalyst and $\text{Cu}(\text{acac})_2$ to promote enantioselective domino oxidation/Michael/reduction reactions between cyclic β -keto esters and allylic alcohols with up to 93% ee.



Scheme 60. Chlorinations of cyclic β -keto esters and *N*-Boc oxindoles [106].



Scheme 61. Paal–Knorr reaction [107].

Excellent results have also been described in miscellaneous reactions, including asymmetric oxidations of alkyl aryl sulfides with 96% ee by using a chiral bis(oxazolinyl)bipyridine iron catalyst reported by Ollevier, asymmetric chlorinations of β -keto esters developed with 92% ee by Che by employing a chiral bipyrrrolidine salan iron complex, as well as a novel general and efficient methodology to synthesize chiral arylpyrroles reported by Tan on the basis of the first catalytic asymmetric Paal–Knorr reaction catalyzed by a combination of iron and a chiral phosphoric acid providing up to 98% ee. In spite of this tremendous progress, asymmetric iron-catalyzed transformations still constitute a young field in comparison to the asymmetric catalysis based on the use of noble metal catalysts. In the near future, this important and promising area is undoubtedly bound to gain greater importance, on the basis of advantages of iron catalysts compared to noble metal ones, including price, availability and toxicity. Indeed, the ever-growing need for environmentally friendly catalytic processes will continue to prompt organic chemists to focus on more abundant transition metals such as iron to develop new catalytic systems. Consequently, a bright future is incontestable for even more sustainable novel and enantioselective iron-catalyzed transformations of all types and their applications in total synthesis.

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