Enantioselective C-H Bond Functionalizations by 3d Transition-Metal Catalysts

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Abstract

Direct catalytic modifications of carbon-hydrogen (C-H) bonds, ubiquitous in organic molecules, represent a powerful strategy in organic synthesis. In the last decade, chemists have focused on the development of sustainable methods for functionalization of inert C-H bonds using cost effective earth-abundant 3d transition-metal catalysts. To fully harness the potential of this technology, however, it is essential to control the stereoselectivity of the C-H functionalization processes. This review describes developments in the emerging area of enantioselective functionalization of C-H bonds by 3d transition-metal catalysts proceeding via inner-sphere C-H activation.

Keywords: C-H functionalization; asymmetric catalysis; 3d transition metals; inner-sphere mechanism; earth abundant

Enantioselective Functionalization of C-H Bonds

The efficient assembly of chiral molecules is a prominent goal of synthetic organic chemistry. Given their abundance in organic molecules, the direct, enantioselective functionalization of C-H bonds offers a powerful solution to this challenging task. In general, this approach uses chiral, transition-metal complexes as catalysts to selectively activate and modify particular C-H bonds. Over the past decade, enantioselective C-H functionalization methodologies have progressed providing new strategies to construct molecular and stereochemical complexity from simple precursors [1, 2]. Among all transition-metals, 4d and 5d elements (in particular palladium, rhodium, ruthenium, and iridium) have dominated the field. Although some of the first examples of enantioselective functionalization of C-H bonds employed chiral copper [3, 4], iron or manganese [5] complexes, methods based on earth-abundant 3d transition metals are still scarce. Recent progress in the development of cost effective and more sustainable 3d metal catalysts has significantly expanded the C-H functionalization toolbox [6]. Despite this headway, exploration of asymmetric processes has lagged behind. This may be attributed to the need for the tailored design of new chiral ligands or an insufficient understanding of the factors affecting the stereoselectivity. Addressing these challenges could deliver not only an attractive alternative to the existing enantioselective noble metal catalysis but also offer unique reactivity patterns reserved for first row transition metals.

Several strategies have been developed for the enantioselective functionalization of C-H bonds, differing in the fundamental mechanism of operation [7, 8]. Processes that do not involve direct interaction between the C−H bond and the metal center are referred to as an outer-sphere or coordination mechanism, include metal-carbenoid and -nitrenoid insertions (Figure 1A) [9], as well as radical transformations operating through hydrogen atom abstraction followed by radical rebound [5] or radical relay [10] mechanisms (Figure 1B and C). The inner-sphere, or organometallic, approach involves a direct interaction of the C-H bond with the transition metal. The following C-H bond cleavage leads to the formation of a discrete organometallic intermediate that undergoes subsequent functionalization. This review focuses on developments in the field of catalytic enantioselective C-H functionalizations by 3d transition-metal catalysts that proceed *via* the inner-sphere C-H activation mechanism (Figure 1D).

Scandium

The first member of 3d transition elements, scandium is a rare earth metal that offers distinctive reactivity towards C-H bonds. In contrast to late transition-metal chemistry, two electron oxidative addition and reductive elimination processes do not take place at scandium centers. Instead, the operative mechanism of scandium catalyzed C-H activations tends to be a concerted four electron four-center process, namely, a **σ-bond metathesis** (see Glossary) [11, 12]. In its most common oxidation state (+3), scandium is highly electropositive, thereby forming polarized Sc-C bonds with alkanes, which are poised to cleave strong, nonpolar C-H bonds. For example, cationic half-sandwich scandium benzyl complexes provide a unique system for catalytic C-6 alkylation of pyridines with terminal olefins [13], a transformation that has proven challenging when employing other transition metals [14, 15]. In 2014, Hou and coworkers reported a scandium complex bearing Cramer`s chiral cyclopentadienyl ligand (Cp^x), **Cat1** [16, 17], that enables the enantioselective C-H addition of substituted pyridines to 1-alkenes (Figure 2) [18]. This process involves the initial formation of an active cationic scandium benzyl species **4**, which is generated in the reaction between the starting **Cat1** and tetra(pentafluorophenyl)borane salt. The subsequent C-H activation of pyridine substrate **1** through a σ-bond metathesis [19] with the cationic scandium complex **4** leads to the key organometallic intermediate **5**. Next, the binaphthyl backbone of the Cp^x ligand induces a specific orientation of the incoming olefin that coordinates to the metal center forming a diastereomeric intermediate **6**. A subsequent 2,1-insertion of the alkene into the Sc-C bond followed by another C-H activation event releases the product and regenerates the pyridine-scandium intermediate **5**. This methodology affords a variety of alkylated pyridine derivatives **3** with good to excellent yields (63-98 %) and enantioselectivities (56-96 % ee).

Iron

Iron catalysis has gained increasing importance in organic synthesis [20], especially in regard to C-H functionalization methodologies [21]. Located in the center of the d-block, iron can adopt both early and late transition-metal character and undergo a wide range of one- and two- electron processes [22]. Until very recently, biological redox processes have been the primary source of inspiration for enantioselective C-H functionalizations under iron catalysis. Iron is present in oxidative enzymes, such as the heme containing cytochrome P-450, which catalyzes oxygenations of a variety of substrates [23]. The desire to emulate these processes *in vitro* led to the development of chiral iron porphyrin complexes for enantioselective C-H oxidations operating through an outer-sphere radical mechanism (Figure 1B) [5]. However,

reports of asymmetric iron catalysis proceeding *via* inner-sphere C-H activation have only recently surfaced.

In 2017, Ackermann and coworkers reported the first iron-catalyzed enantioselective C-H functionalization process by the inner-sphere activation mechanism (Figure 3A) [24, 25]. Design of a new N-heterocyclic carbene (NHC) ligand **L1** featuring meta-substitution on an *N*,*N*-diaryl moiety enabled highly enantioselective imine directed alkylation of indole derivatives **8** with vinylferrocenes and styrenes **9**. The reaction is initiated by reduction of the iron(III) precursor by a Grignard reagent (CyMgCl) to generate the active iron catalyst. Coordination of an alkane to the NHC-iron complex **11** followed by **migratory insertion**, induced by ligation of the substrate, gives intermediate **13**. Mechanistic investigations suggested that the inner-sphere C-H metalation step occurs through a **ligand-to-ligand hydrogen transfer** (LLHT- **I**) [26] from the indole substrate **8** to the terminal position of the alkene. A plausible stereoinduction model at the enantiodetermining migratory insertion step has been proposed (please see [24]). Similar reactivity has been previously achieved employing cobalt [27, 28] and iridium [29] catalysis, however only the former one provides a useful level of enantiocontrol (Figure 4B).

In the same year, Butenschön and Schmiel disclosed an iron-catalyzed ortho-alkylation and arylation of ferrocene derivatives **14** bearing a bidentate ortho- directing group (Figure 3B) [30]. A screening of commercially available chiral *P*,*P*-ligands indicated (*R*,*R*)-Chiraphos as a promising scaffold to control the enantioselective arylation process. Although further optimization is needed this report is an encouraging first example of enantioselective iron-catalyzed C-H activation guided by chiral phosphine ligands.

Cobalt

Cobalt complexes are versatile catalysts in the context of C-H activation [31, 32]. Both low-valent cobalt catalysts, often generated by *in situ* reductions of simple cobalt(II) salts, and bench stable high-valent cobalt(III) complexes have attracted significant attention. The first application of a low-valent cobalt catalyst in asymmetric C-H functionalization provided a valuable alternative to previously reported rhodium-catalyzed enantioselective hydroacylation of ketones and terminal olefins [33, 34]. In 2014, Yoshikai and Yang disclosed a cobalt-chiral diphosphine catalytic system for intramolecular hydroacylations of 2-acylbenzaldehyde and 2-alkenylbenzaldehyde derivatives (Figure 4A) [35]. The corresponding enantioenriched phthalides **17** and indanones **18** were obtained with good to

excellent yields and enantioselectivities demonstrating the capability of chiral cobalt complexes to conduct enantioselective processes previously reserved for noble metal catalysis. Three years later the same group extended the scope of this transformation to the largely unexplored [36] hydroacylation of trisubstituted alkenes **19** [37]. The resulting 2,3-disubstituted indanes **20** were isolated with high yields (66-99 %) and good to excellent diastereo- (3.1:1- 20:1 dr) and enantiocontrol (11-98 % ee) irrespective of the E/Z geometry ratio of starting olefin substrates. Shortly after, Dong and coworkers disclosed the enantioselective intramolecular hydroacylation process for the construction of the strained four-membered ring scaffold **22** in preference to the five-membered ring product **23** [38]. The desymmetrization of aliphatic aldehydes by the cobalt catalyst bearing chiral bidentate phosphine ligand (*S*,*S*)-BDPP leads to cyclobutanones possessing quaternary and tertiary stereogenic centers with high yields (60- 93 %) and high stereoselectivity (10:1- 20:1 dr and 64-96 % ee). The cobalt catalyzed hydroacylations are believed to operate through an analogous mechanism to the better-understood rhodium-catalyzed process [39]. Initially, the reduction of a cobalt(II) salt, in the presence of chiral phosphine ligand, generates the active cobalt(I) diphosphine species. Oxidative addition of the aldehyde C-H bond would lead to acyl-(hydrido)cobalt intermediate **24** that can undergo a stereocontrolled migratory insertion to afford a 6-membered cobaltacycle **25**. A subsequent carbon-carbon or carbon-oxygen bond forming reductive elimination would assemble the chiral indanone and phthalide scaffolds.

Enantioselective low-valent cobalt catalysis has also found application in an imine-directed C-H alkylation of indole derivatives with styrenes (Figure 4B). [27] The *in situ* generated cobalt catalyst, bearing a chiral phosphoramidite ligand **L2**, allowed functionalization of *N*-methyl indole substrate (**26** R^2= Me) with good yield (83 %) but low enantiocontrol (47 % ee). Further optimizations indicated a significant influence of the *N*-substituent on the enantioselectivity. Boc protected indoles (**26** R^2= Boc) were selected as optimal substrates to provide alkylated products **28** with good yields (16-90 %) and moderate enantioselectivities (58-86 % ee). In contrast to the iron-catalyzed alkylation of indoles discussed previously (Figure 3A), the active cobalt catalyst was proposed to activate the C-H bond through an oxidative addition mechanism. The authors suggested that both the migratory insertion and reductive elimination steps influence the enantioselectivity of the process.

Sato and coworkers disclosed a cobalt-based catalytic system for the direct addition of allylic C-H bonds to ketones (Figure 4C) [40]. The key low valent allylcobalt(I) intermediate **34**, formed after a C-H activation step assisted by $AlMe_3$, has nucleophilic character that allows

direct C-H addition to carbonyls [41]. This strategy provides new opportunities to well-studied allylic C-H functionalizations by high valent palladium [42] and rhodium [43] catalysts that involve electrophilic η^3-allylmetal intermediates. Although the work focuses mostly on the racemic transformation between allyl arenes and various ketones, the authors demonstrated that chiral (*R*)-Difluorphos ligand affords the homoallylic alcohol product **33** with promising enantioselectivity (81 % ee), albeit with a diminished yield (25 %). Notably, optimization studies indicated that Co catalysts are superior to rhodium complexes.

A different strategy has been applied to achieve enantioselective C-H functionalization by high valent-cobalt(III) complexes. The cobalt(III) catalysts activate C-H bonds in non-oxidative pathways through a **concerted metalation–deprotonation** (CMD) [44] mechanism or by an intermolecular **single electron transfer** (SET) process [45], both of which are substantially different to the oxidative C-H activation by low-valent cobalt complexes. The CMD mechanism involves the cooperative action of the metal with a base cocatalyst, such as a carboxylate anion. This brings new opportunities to dictate the stereoselectivity of C-H functionalization processes by means of a chiral carboxylate cocatalyst [46-51]. In this context, Ackermann and coworkers recently developed an enantioselective C-H alkylation reaction catalyzed by an achiral high-valent pentamethylcyclopentadienyl (Cp^*) cobalt(III) complex and chiral carboxylic acid (Figure 4D) [52, 53]. Design of a new C-2 symmetric chiral carboxylic acid cocatalyst **L3** was essential to perform the pyridine directed C-H alkylation of indoles **36** by allyl arenes **37** with moderate yields (41-73 %) and good enantioselectivities (70-86 % ee). Mechanistic investigations revealed a considerable negative **nonlinear-effect** (NLE) [54] that was rationalized by formation of a hydrogen-bond-stabilized dimeric resting state of the chiral ligand. The NLE was not observed when using Amberlyst 15 as an additive, which was instrumental in improving the reaction efficiency.

Shortly after, Matsunaga and coworkers disclosed a cobalt(III) catalyzed asymmetric C(sp^3)-H amidation of thioamides exploiting the concept of a chiral acid assisted enantioselective C-H functionalization (Figure 4E) [55]. The previously reported studies on the racemic process suggest the CMD mechanism being operative for the C-H activation step [56]. Following this precedence, Matsunaga and coworkers developed a new chiral carboxylic acid **L4** that enabled isolation of amidated thioamides **41** with high yields (50-99 %) and good enantioselectivities (78-88 % ee). Deuterium labeling studies indicated that the C-H activation is an irreversible, enantiodetermining step.

Nickel

Nickel catalysis offers diverse reactivity patterns beyond the traditional framework of noble metals. The easy accessibility of oxidation states ranging from 0 to +3 enable a variety of transformations engaging Ni(0)/Ni(II), Ni(I)/Ni(III) or Ni(I)/Ni(II)/Ni(III) catalytic cycles [57]. To date, a few reports involving activation of C-H bonds by chiral nickel(0) catalysts have also been disclosed.

In 2013, Cramer and Donets reported the first enantioselective C-H functionalization process employing chiral nickel/Lewis acid bimetallic catalysis (Figure 5A) [58-60]. The development of a new class of chiral diaminophosphine oxide ligands **L5** allowed the asymmetric hydrocarbamoylation of alkenes, a transformation that had remained elusive until then. The major obstacle to this process stems from the low reactivity of the formamide C-H bond towards transition metal insertion. Many phosphine ligands were shown to be ineffective in promoting this transformation. A single exception to this was observed, that was eventually attributed to a phosphine oxide impurity acting as a ligand. This discovery led to the development of novel, easily tunable, chiral diaminophosphine oxides ligands, among which **L5** was found optimal. Finally, the resulting pyrrolidone products **44** were accessed with high yields (46-98 %) and enantioselectivities (79-95 % ee). The suggested mechanism first involves attack of the phosphinous acid tautomer of the ligand on $AlMe_3$ to form intermediate **46**. Next, the nickel precursor ($Ni(cod)_2$) coordinates to the phosphorus atom to generate the bimetallic complex **47**. The electrophilic aluminium center activates the carbonyl group of the formamide and forms intermediate **48**. A subsequent C-H oxidative addition to nickel center generates the nickel hydride species **49** that undergoes migratory insertion to the olefin forging a new stereogenic center. The following reductive elimination liberates the enantioenriched lactam product **44** and the bimetallic catalyst **47**.

In 2018, Ye and coworkers applied the nickel/Lewis acid bimetallic catalysis to perform an intramolecular enantioselective C−H cyclization of imidazoles with alkenes (Figure 5B). [61] After screening a variety of chiral ligands, it was observed that the Taddol-derived phosphinoxide **L6** was the best performing ligand to enable the synthesis of polycyclic imidazoles **52** with exclusive *exo*-selectivity, high yields (65-92 %) and enantioselectivities (80-99 % ee). The reaction starts from the formation of an active Ni/Al bimetallic complex bearing a chiral phosphine oxide ligand that activates the C-H bond through either a LLHT or oxidative addition mechanism upon coordination of the imidazole substrate to the aluminum

center **53**. The subsequent reductive elimination releases the product **52** and the bimetallic active catalyst. This strategy represents an important alternative to previously reported *exo*-selective rhodium catalyzed enantioselective C-H alkylation of imidazoles, which requires rather harsh reaction conditions (135-175 ˚C) [62].

Ackermann and coworkers reported a complementary approach that enables the enantioselective C-H cyclization of imidazoles with complete *endo*-selectivity (Figure 5C) [63]. The bidentate JoSPOphos type ligand **L7**, previously explored in asymmetric rhodium catalysis [64-66], was highly successful, even in the absence of $AlMe_3$. This simple catalytic system allows the assembly of imidazole products **55**, containing a chiral six-member ring, with high yields (53-96 %) and enantiomeric excesses (84-98 % ee). Obviating the need for $AlMe_3$ in the catalytic system helped to improve the functional group tolerance. Furthermore, this method allowed the synthesis of various biologically relevant nitrogen-containing heterocycles. Additional kinetic and deuterium labeling studies shined a light on the mechanism in operation suggesting the LLHT as the C-H activation step. The absence of NLE indicated the involvement of mono-ligated nickel catalyst in the process.

Nickel catalysis has been exploited for the direct C-H alkylation of other important heterocycles [6] including pyridones [67, 68]. In 2015, Cramer and Donets demonstrated ligand-controlled regiodivergency in the intramolecular C6 alkylation of pyridones with olefins (Figure 5d) [69]. The use of two complementary sets of ligands allowed selective access to both the *exo*- and *endo*-cyclization modes. Simple cyclooctadiene promotes an *exo*-selective cyclization, whereas a bulky NHC results in an *endo*-selective mode. Preliminary attempts to render the *exo*-cyclization enantioselective, through the use of chiral diene ligands, failed. The *endo*-product, however, could be obtained in an enantioselective manner when employing chiral NHC ligand **L8**, albeit with moderate enantiocontrol (57 % ee). Further intensive studies, exploiting a large number of NHC ligands, led to the development of new structural analogs of chiral carbene reported by Gawley and coworkers [70, 71]. **L9** was selected as the optimal ligand to conduct the enantioselective *endo*-cyclization with high yields (32-90 %) and enantiocontrol (50-98 % ee) [72]. This report is a single example of highly enantioselective C-H functionalization of pyridones [73].

NHC ligands have been found to be essential in three component reductive couplings, of aromatic aldehydes with norbornenes, and silanes, which proceeds through aromatic C-H bond activation of aryl aldehydes [74]. In 2016, Cramer and Ahlin disclosed a procedure to

conduct this annulation process in a highly stereoselective manner (Figure 5E) [75]. Screening of a variety of chiral NHC ligands indicated a promising performance of Grubbs's C2-symmetric imidazolidin-2-ylidene **L10** (99 %, 43 % ee). Further optimization of this structure led to a new bulky C2-symmetric NHC ligand based on the 1,2-di(napthalen-1-yl)ethylene diamine backbone **L11** giving the desired product in 74 % yield with 86 % ee. The resulting indanol derivatives **64** were isolated as single diastereoisomers with good yields (25-93 %) and enantioselectivities (69-91 % ee).

Copper

Copper has remarkably rich chemistry that has found numerous applications in the C-H functionalization technology. As a late transition-metal, copper occurs in oxidization states ranging from 0 to +4. The most common Cu(I), Cu(II) and Cu(III) are primarily responsible for the well-established copper chemistry involving one- and two-electron transfer processes [76]. The field of enantioselective C-H functionalization has mostly benefited from copper catalyzed transformations operating through the outer-sphere C-H activation mechanism. These include C-H insertion into copper carbenoid complexes [9, 77] and atroposelective dimerization of electron rich arenes [78, 79] proceeding through a SET mechanism [80]. Substantial efforts have been made to develop a highly enantioselective Kharasch–Sosnovsky reaction [81-83], the mechanism of which is still under debate [84]. Additionally, recent advances in copper radical chemistry have also provided new strategies for enantioselective functionalization of C-H bonds through a hydrogen atom transfer (HAT) radical relay mechanism (Figure 1C) [10, 85, 86].

Transformations that operate through the inner-sphere mechanism involving direct copper insertion into a C-H bond are scarce. An example that could qualify into this category includes reaction proceeding through a base assisted cupration of C-H bonds. Sawamura and coworkers disclosed the enantioselective allylic alkylation of azoles by utilizing chiral copper NHC catalysis (Figure 6) [87]. Various benzothiazole and benzoxazole **66** substrates were converted into their allylic analogs containing quaternary all carbon stereogenic centers in the reaction with δ,δ-disubstituted primary allylic phosphates **67**. Development of a new NHC ligand **L12** bearing a naphtholic hydroxy group was essential to conduct the process with good efficiencies (16-87 %) and selectivities (69-92 % ee). Based on the analogy to the racemic reaction reported by the same group [88], the mechanism could involve initial formation of an active organocopper species generated in the reaction between a copper

catalyst and an excess of LiO*t*Bu base. The LiO*t*Bu was found to not be basic enough to lithiate the (hetero)arene substrate. The LiO*t*Bu-assisted C-H activation step would generate a heterocuprate intermediate **69** that could react with the allylic phosphate substrate in a subsequent oxidative addition, reductive elimination sequence to form the product **68**.

Concluding Remarks and Future Perspectives

Over the last six years, new methods for enantioselective functionalization of C-H bonds have emerged creating exciting opportunities for expanding the scope of this field beyond precious 4d and 5d transition metals. These early studies have demonstrated the tremendous, yet untapped potential of 3d metal complexes to control stereoselectivity in various processes operating through the inner-sphere C-H activation mechanism providing a few attractive alternatives as well as complementary reactivities to the established asymmetric noble metal catalysis.

Being still in its infancy, enantioselective C-H functionalization by 3d transition metal catalysts holds great promise for providing more sustainable technology for the construction of chiral molecules (see Outstanding Questions). A diversity of existing chiral ligand families offers tantalizing opportunities to explore their potential in a rapidly growing number of transformations catalyzed by first row transition metals. However, a better mechanistic understanding of these organometallic systems is likely to significantly assist the progress of this field. In contrast to C-H functionalizations with 4d and 5d metals, which mostly involves two-electron transfer processes, mechanisms of first row transition metals are more diverse and are often prone to engage in SET events. Gaining further insight into the reactivity modes could allow a more rational design of improved chiral ligands geared towards the desired reactivity. Future work could strive to engage other chiral 3d metal complexes to modify C-H bonds through the inner-sphere activation pathway stereoselectively. Recent advances in electrocatalysis [89] as well as photocatalysis [90] allow for discrete modulation of metal oxidation states and can become design elements for new C-H functionalization processes. In the future, high-throughput screening technology paired with machine-learning approaches can have important contributions to shorten catalyst discovery and ligand optimization timelines [91]. We expect that further advances in the development of new methods for enantioselective functionalization of C-H bonds by earth abundant 3d transition metals will deliver new sustainable synthetic tools for efficient assembly of relevant chiral molecules.

During the revision of this manuscript, three new reports of enantioselective C-H bond functionalization by nickel catalysts [92] and high-valent cobalt complexes were disclosed, [93-94] underlining the increasing pace of discovery in this exciting field.

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Figure Captions.

Figure 1. General mechanisms for transition-metal catalyzed C–H bond functionalization. (A-C) C-H activation occurs without direct interaction of the metal center with the C-H bond: outer-sphere mechanism. (D) C-H activation through a direct metal insertion into the C-H bond: inner-sphere mechanism. [M], transition-metal; L^*, chiral ligand.

Figure 2. Scandium-catalyzed enantioselective functionalization of C-H bonds. C-H bond addition of pyridines to alkenes catalyzed by a scandium complex bearing a Cp^x ligand. TIPS, triisopropylsilyl; Cp^x, chiral cyclopentadienyl ligand.

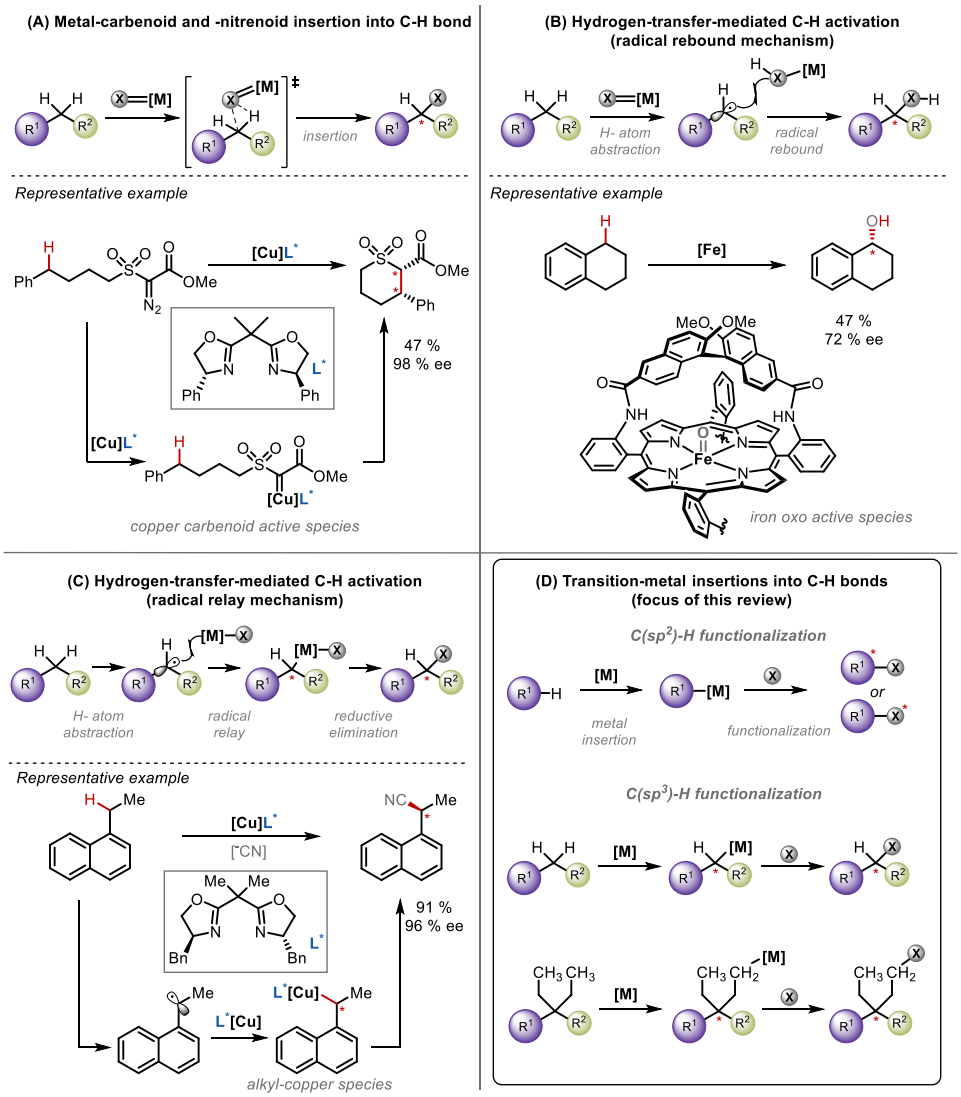
Figure 3. Iron-catalyzed enantioselective functionalization of C-H bonds. (A) Asymmetric alkylation of indoles enabled by a novel *N*-heterocyclic carbene ligand. (B) An example demostrating the potential of chiral diphosphine ligands in iron catalzed asymmetric C-H functionalization. PMP, *p*-methoxyphenyl; Fc, ferrocenyl; LLHT, ligand-to-ligand hydrogen transfer; acac, acetylacetone; TMEDA, tetramethylethylenediamine; DCB, 2,3-dichlorobutane; L^*, chiral ligand.

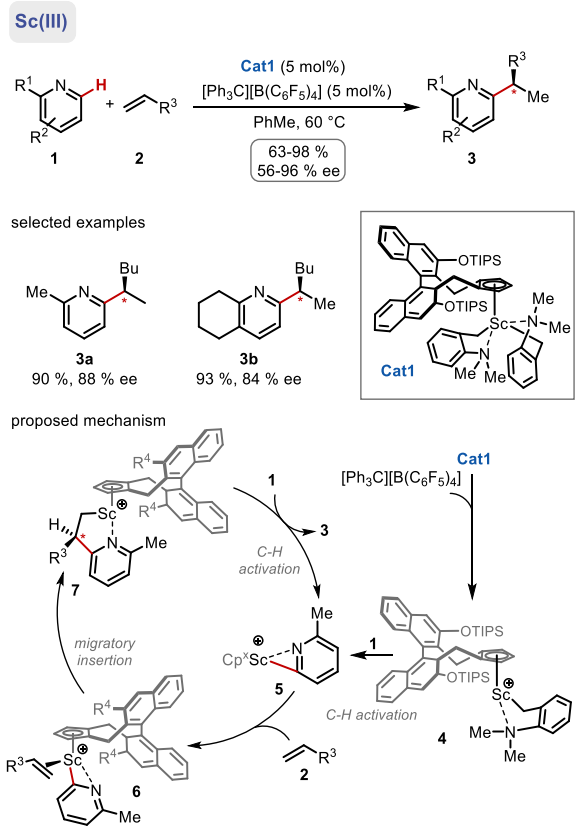
Figure 4. Cobalt-catalyzed enantioselective functionalization of C-H bonds. (A-C) Low-valent cobalt catalysis, (D-E) high-valent cobalt catalysis. (A) Asymmetric hydroacylations of ketones and olefins by cobalt-chiral diphosphine complexes. (B) A cobalt-chiral phosphoramidite catalyst enables imine-directed alkylation of indoles. (C) An example of asymmetric addition of an allylic C(sp^3)-H bond to acetone enabled by a chiral cobalt catalyst. **(**D) Asymmetric C-H alkylation of indoles by cobalt/chiral carboxylic acid catalysis; branched : linear selectivities in parentheses. (E) Cobalt/chiral carboxylic acid enabled asymmetric C(sp^3)-H amidation of thioamides. Acac, acetylacetone; PMP, *p*-methoxyphenyl; Cp*, pentamethylcyclopentadienyl; oDCB, 1,2-dichlorobenzene; CMD, concerted metalation-deprotonation; L^*, chiral ligand.

Figure 5. Nickel-catalyzed enantioselective functionalization of C-H bonds. (A) A new class of diaminophosphine oxide ligands enables nickel/Lewis acid-catalyzed asymmetric hydrocarbamoylations of alkenes. (B) Chiral nickel/Lewis acid bimetallic catalysis for *exo*-selective C-H cyclization of imidazoles with alkenes. (C) *Endo*-selective C-H cyclization of imidazoles with alkenes by a chiral nickel/JoSPOphos manifold. (D) A bulky chiral NHC ligand allows a highly enantioselective C-H alkylation of pyridones. (E) Asymmetric three-component coupling catalyzed by chiral nickel/NHC catalyst. Cod, 1,5-cyclooctadiene; LLHT, ligand-to-ligand hydrogen transfer; MAD, methylaluminum bis(2,6-di-tert-butyl 4-methylphenoxide); Mes, mesityl; L^*, chiral ligand; TIPS- triisopropylsilyl.

Figure 6. Copper-catalyzed enantioselective functionalization of C-H bonds. C-H alkylation of azoles enabled by chiral copper/NHC catalyst. Branched : linear selectivity in parentheses. L^*- chiral ligand.

Figures.


(A) Metal-carbenoid and -nitrenoid insertion into C-H bond
insertion
Representative example
[Cu]L*
47 %
98 % ee
copper carbenoid active species
(B) Hydrogen-transfer-mediated C-H activation
(radical rebound mechanism)
H- atom abstraction
radical rebound
Representative example
[Fe]
47 %
72 % ee
iron oxo active species
(C) Hydrogen-transfer-mediated C-H activation
(radical relay mechanism)
H- atom abstraction
radical relay
reductive elimination
Representative example
[Cu]L*
[-CN]
91 %
96 % ee
alkyl-copper species
(D) Transition-metal insertions into C-H bonds
(focus of this review)
C(sp2)-H functionalization
metal insertion
functionalization
or
C(sp3)-H functionalization



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639

640

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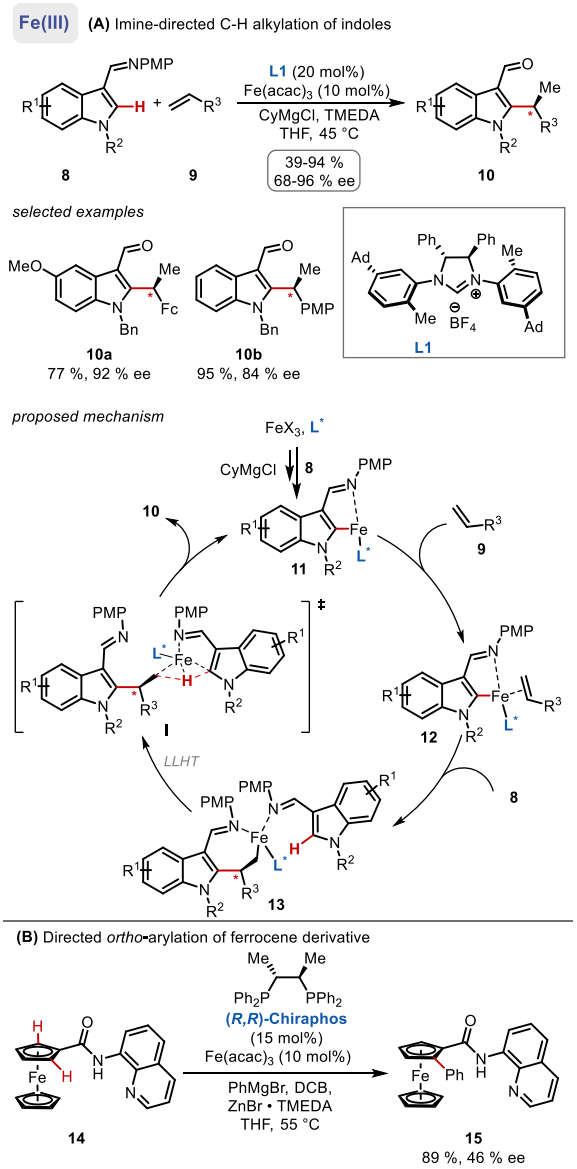
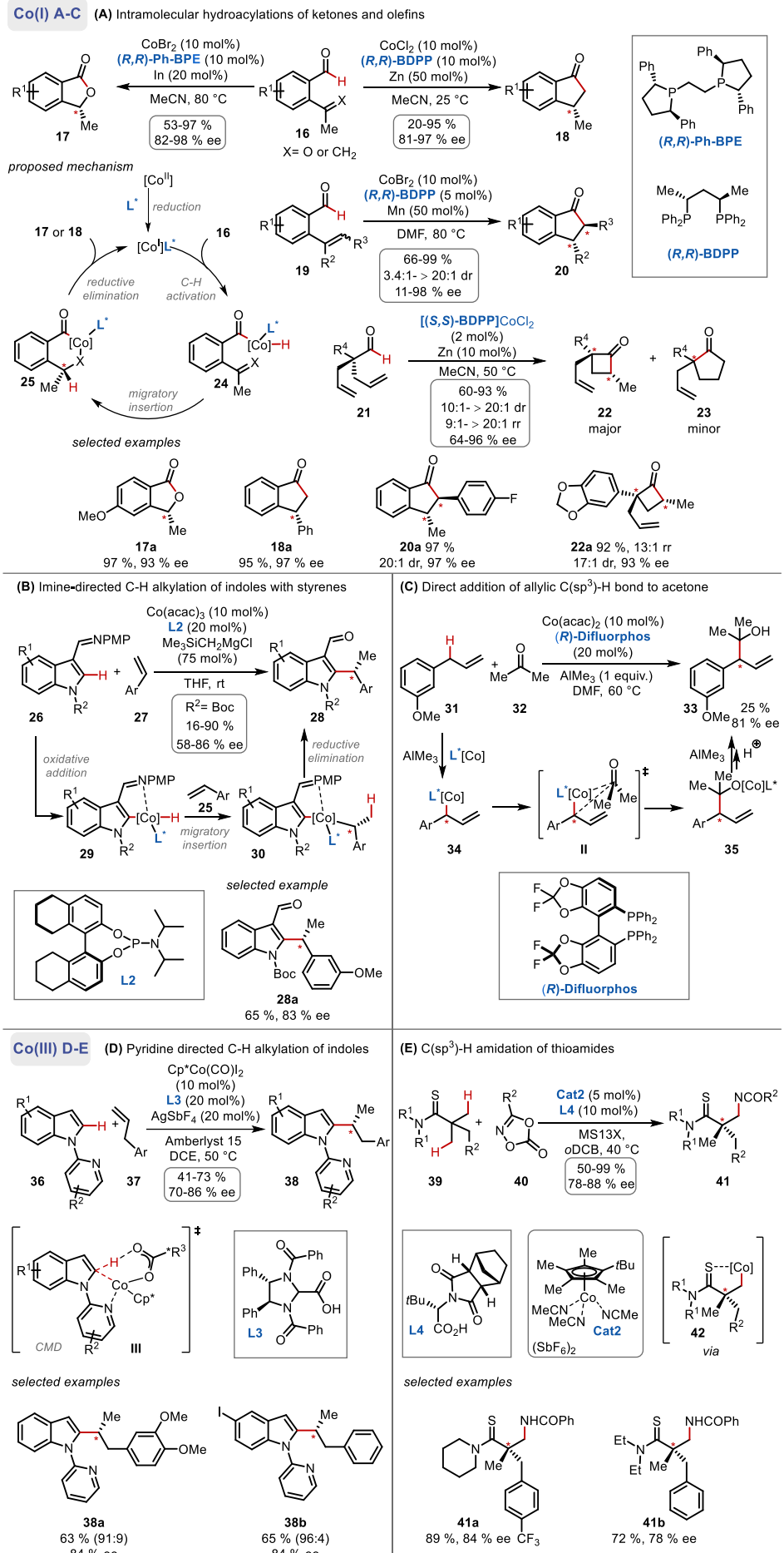
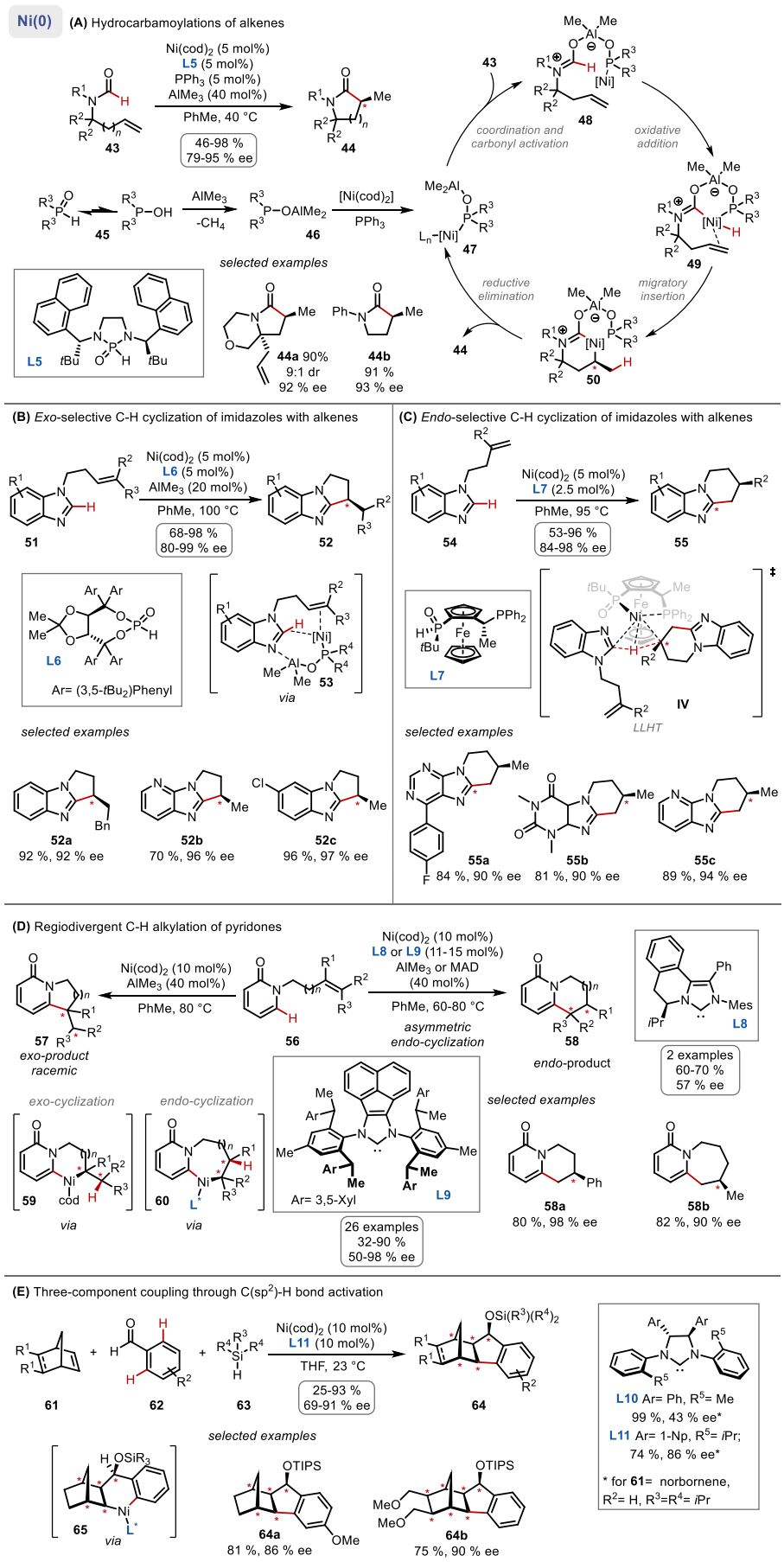
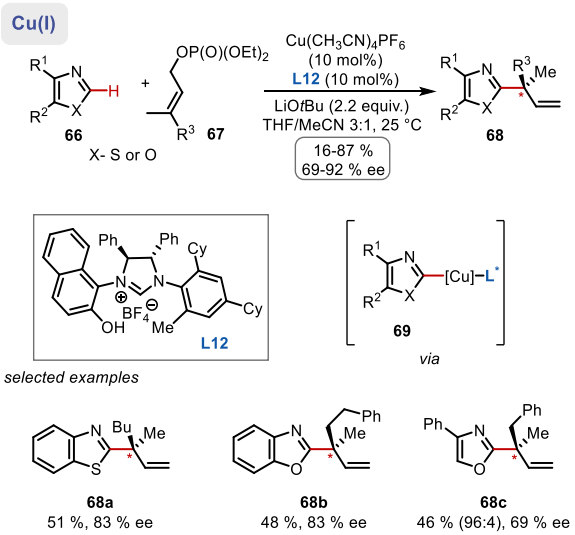

Fe(III)
(A) Imine-directed C-H alkylation of indoles
L1 (20 mol%)
Fe(acac)3 (10 mol%)
CyMgCl, TMEDA
THF, 45 °C
39-94 %
68-96 % ee
8
9
10
selected examples
10a
77 %, 92 % ee
10b
95 %, 84 % ee
L1
proposed mechanism
FeX3, L*
CyMgCl
11
12
13
I
LLHT
(B) Directed ortho-arylation of ferrocene derivative
(R,R)-Chiraphos
(15 mol%)
Fe(acac)3 (10 mol%)
PhMgBr, DCB,
ZnBr • TMEDA
THF, 55 °C
14
15
89 %, 46 % ee


Co(I) A-C
(A) Intramolecular hydroacylations of ketones and olefins
CoBr2 (10 mol%)
(R,R)-Ph-BPE (10 mol%)
In (20 mol%)
MeCN, 80 °C
53-97 %
82-98 % ee
CoCl2 (10 mol%)
(R,R)-BDPP (10 mol%)
Zn (50 mol%)
MeCN, 25 °C
20-95 %
81-97 % ee
X= O or CH2
(R,R)-Ph-BPE
(R,R)-BDPP
proposed mechanism
reduction
reductive elimination
C-H activation
CoBr2 (10 mol%)
(R,R)-BDPP (5 mol%)
Mn (50 mol%)
DMF, 80 °C
66-99 %
3.4:1- > 20:1 dr
11-98 % ee
[(S,S)-BDPP]CoCl2
(2 mol%)
Zn (10 mol%)
MeCN, 50 °C
60-93 %
10:1- > 20:1 dr
9:1- > 20:1 rr
64-96 % ee
migratory insertion
selected examples
17a
97 %, 93 % ee
18a
95 %, 97 % ee
20a 97 %
20:1 dr, 97 % ee
22a 92 %, 13:1 rr
17:1 dr, 93 % ee
major
minor
(B) Imine-directed C-H alkylation of indoles with styrenes
Co(acac)3 (10 mol%)
L2 (20 mol%)
Me3SiCH2MgCl
(75 mol%)
THF, rt
R2= Boc
16-90 %
58-86 % ee
oxidative addition
reductive elimination
migratory insertion
selected example
28a
65 %, 83 % ee
(C) Direct addition of allylic C(sp3)-H bond to acetone
Co(acac)2 (10 mol%)
(R)-Difluorphos
(20 mol%)
AlMe3 (1 equiv.)
DMF, 60 °C
25 %
81 % ee
(R)-Difluorphos
Co(III) D-E
(D) Pyridine directed C-H alkylation of indoles
Cp*Co(CO)I2
(10 mol%)
L3 (20 mol%)
AgSbF4 (20 mol%)
Amberlyst 15
DCE, 50 °C
41-73 %
70-86 % ee
CMD
selected examples
38a
63 % (91:9)
84 % ee
38b
65 % (96:4)
84 % ee
(E) C(sp3)-H amidation of thioamides
Cat2 (5 mol%)
L4 (10 mol%)
MS13X,
oDCB, 40 °C
50-99 %
78-88 % ee
via
selected examples
41a
89 %, 84 % ee
41b
72 %, 78 % ee


Ni(0)
(A) Hydrocarbamoylations of alkenes
Ni(cod)2 (5 mol%)
L5 (5 mol%)
PPh3 (5 mol%)
AlMe3 (40 mol%)
PhMe, 40 °C
46-98 %
79-95 % ee
43
44
AlMe3
-CH4
[Ni(cod)2]
PPh3
45
46
47
48
49
50
coordination and carbonyl activation
oxidative addition
migratory insertion
reductive elimination
selected examples
L5
44a 90%
9:1 dr
92 % ee
44b
91 %
93 % ee
(B) Exo-selective C-H cyclization of imidazoles with alkenes
Ni(cod)2 (5 mol%)
L6 (5 mol%)
AlMe3 (20 mol%)
PhMe, 100 °C
68-98 %
80-99 % ee
51
52
L6
Ar= (3,5-tBu2)Phenyl
53
via
selected examples
52a
92 %, 92 % ee
52b
70 %, 96 % ee
52c
96 %, 97 % ee
(C) Endo-selective C-H cyclization of imidazoles with alkenes
Ni(cod)2 (5 mol%)
L7 (2.5 mol%)
PhMe, 95 °C
53-96 %
84-98 % ee
54
55
L7
IV
LLHT
selected examples
55a
84 %, 90 % ee
55b
81 %, 90 % ee
55c
89 %, 94 % ee
(D) Regiodivergent C-H alkylation of pyridones
Ni(cod)2 (10 mol%)
AlMe3 (40 mol%)
PhMe, 80 °C
57
exo-product
racemic
56
Ni(cod)2 (10 mol%)
L8 or L9 (11-15 mol%)
AlMe3 or MAD
(40 mol%)
PhMe, 60-80 °C
asymmetric
endo-cyclization
58
endo-product
2 examples
60-70 %
57 % ee
L8
exo-cyclization
endo-cyclization
59
60
via
L9
Ar= 3,5-Xyl
26 examples
32-90 %
50-98 % ee
selected examples
58a
80 %, 98 % ee
58b
82 %, 90 % ee
(E) Three-component coupling through C(sp2)-H bond activation
Ni(cod)2 (10 mol%)
L11 (10 mol%)
THF, 23 °C
25-93 %
69-91 % ee
61
62
63
64
L10 Ar= Ph, R5= Me
99 %, 43 % ee*
L11 Ar= 1-Np, R5= iPr;
74 %, 86 % ee*
* for 61= norbornene,
R2= H, R3=R4= iPr
selected examples
65
via
64a
81 %, 86 % ee
64b
75 %, 90 % ee

653



Highlights

The increasing interest in chemical utilization of earth-abundant 3d transition-metals have led to the development of new, sustainable methods for functionalization of C-H bonds.

To fully realize the potential of 3d transition-metals in the modification of C-H bonds, chemists have to control the stereochemistry of the C-H functionalization processes.

3d transition-metal catalysts can provide valuable alternatives to enantioselective C-H functionalizations by 4d and 5d metals.

The unique chemistry of 3d elements offers exciting opportunities for the development of new enantioselective C-H functionalization processes beyond the scope of asymmetric noble metal catalysis.

Glossary

σ-Bond metathesis: a concerted exchange of a metal-ligand σ-bond with a σ-bond of incoming substrate.

Concerted metallation-deprotonation (CMD): a metal/base promoted C-H bond cleavage that occurs by a simultaneous metalation and deprotonation processes.

Ligand-to-ligand hydrogen transfer (LLHT): a C-H bond activation mechanism, which can be viewed as a concerted C-H oxidative addition migratory insertion process. LLHT does not involve metal hydrides species.

Nonlinear effect: a phenomena in asymmetric catalysis describing the deviation from the proportionality between the enantiomeric excess of the chiral ligand and the enantioselectivity of the generated product.

Migratory insertion: insertions of an unsaturated ligand into an adjacent metal-ligand bond.

Single electron transfer (SET): the transfer of a one single electron from a molecular entity to another, or between two localized sites in the same molecular entity.

Outstanding Questions Box

How can we improve the design of chiral ligands for 3d transition-metal catalysis?

How can we incorporate all 3d elements in enantioselective C-H functionalization methodology?

How can we merge the chemistry of 3d transition-metals with recent technological advances to develop new enantioselective C-H functionalization processes?

Is it possible to cover almost the entire range of enantioselective modifications of C-H bonds with cost-effective, earth-abundant 3d transition-metal catalysts?

Will enantioselective C-H functionalization by 3d transition-metals become a common strategy for the construction of chiral molecules?