Transient ligand-enabled transition metal-catalysed C-H functionalisation

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Dedication ((optional))

Abstract: Transition metal-catalysed C-H bond functionalisation is one of the most efficient and powerful strategies in synthetic organic chemistry to derivatize otherwise inert sites of organic molecules for the construction of C-C and C-heteroatom bonds. However, additional steps are often required in order to install the directing groups to realize the selective C-H bond functionalisation of the substrates. These tedious steps run counter to the step-economical nature of the C-H activation. In contrast, direct functionalisation of the substrate, utilizing the transient ligands, avoids the unnecessary steps for the pre-functionalisation of the substrates. In this mini review, we will provide a short journey for the major progress made in this field for the C-H functionalisation on sp^2 and sp^3 carbon centres with different transient working modes, including covalent, hydrogen, and ionic bonds.

1. Introduction

Transition metal-catalysed C-H bond functionalisation has emerged as one of most efficient method for selective carbon-carbon and carbon-heteroatom bond construction in recent years. Despite the great progress, two challenges still exist in the direct C-H functionalisation methods: the inert nature of most C-H bonds and the multiple analogous C-H bonds in selective reactions.[1] In order to solve these issues, the directing group strategy has been raised as a powerful tool for the site-selective C-H functionalisation. Although transition metal-catalysed selective functionalisation of either C(sp^2)-H or C(sp^3)-H bonds has been well developed by employing various directing groups on substrates,[2] there is a major issue in the synthetic application of this method: the directing group pre-installation and removal. Additional steps are often required for the pre-construction of the substrates and for the removal of the directing groups, which diminishes the efficiency and compatibility of the reactions.[3] Clearly, there is a need to develop novel methods for transition metal-catalysed C-H bond functionalisation reactions. A promising approach would be the utilization of a transient ligand which can bind to the substrate and coordinate to the metal centre in a reversible fashion. In this

process, the desired site-selective C-H bond functionalisation would be accomplished with a catalytic amount of this transient ligand without changing the substrate structure after the catalysis has finished. To this catalytic cycle, an efficient transient ligand will be temporarily and reversibly installed on the substrate to form intermediate **I** via a reversible covalent bond or non-covalent bond. Then, this intermediate **I** will interact selectively with the transition metal catalyst, after the monodentate or bidentate coordination of the transition metal with the transient ligand, thus forming the corresponding metallacycle intermediate **II**. Then intermediate II reacts with the coupling reagent leading to the intermediate **III**, followed by the construction of the intermediate **IV** and the regeneration of the transition metal catalyst. Finally, the removal of the transient ligand affords the desired product (Scheme 1). Overall, this whole process occurs in a single reaction pot. To be mentioned, elaborated reviews on transient directing group enabled C-H functionalisation have been released by Besset, Ackermann, Maiti, and Bull.[4]

In this mini-review, we will emphasize and discuss the remarkable progress made in the field using the reversible covalent bond mode, focusing on transient imine, enamine and phosphite directing groups. We will also briefly discuss the transient ligand strategy using the non-covalent bonding modes, such as the hydrogen and ionic bonds for C-H activation. As a result, we have categorized the entire theme into two parts: the reversible covalent bond and non-covalent bond modes.

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Scheme 1. Concept of transient ligand-promoted catalytic C-H functionalisation

Ben Niu was born in 1990, in Jiaozuo, P. R. of China. In 2012, he first completed his B.S. degrees at Henan Institute of Science and Technology. After obtaining his M.S. degrees in pharmaceutical engineering from Jiangsu University in 2015. In July 2016, He is currently a Ph.D. student under the supervision of Professor Haibo Ge at the Department of Chemistry and Chemical Biology, Indiana University – Purdue University Indianapolis (IUPUI). His research focuses on novel organic transformations based on transition metal-catalysed C-H activation.

Ke Yang was born in Jiangsu Province, P. R. of China. He completed his B.S. and M.S. degrees at Jiangsu Normal University. Next, he obtained his PhD degree from Nanjing University under the supervision of Professor Yan Zhang. From 2014, he became a postdoctoral fellow at Nanjing Unversity with Professor Guigen Li. In 2015, he joined in the group of Professor Haibo Ge at the Department of Chemistry and Chemical Biology, Indiana University – Purdue University Indianapolis (IUPUI) in USA. Two years later, he moved to Changzhou University and began his independent academic career. His research interests involve novel transition metal-catalysed C-H bond functionalisation reactions.

Brianna Lawrence was born in Greenwood, Indiana. She is currently working on her bachelor's degree in applied mathematics with a secondary area of study in chemistry. She started organic chemistry research in the summer of 2018 after becoming interested due to taking organic chemistry in college with Professor Haibo Ge. Now, she is working in his organic chemistry lab and helping to research transition metal-catalysed C-H bond functionalisation reaction and electrochemical reactions.

Haibo Ge received his Ph.D. degree in Medicinal Chemistry from The University of Kansas in 2006 with Professor Gunda Georg. He then moved to The Scripps Research Institute for postdoctoral study with Professor Dale Boger. In 2009, he began his independent academic career at the Department of Chemistry and Chemical Biology at Indiana University – Purdue University Indianapolis. Research in his group is mainly focused on the development of novel methods for carbon–carbon and carbon–heteroatom bond formation through transition metal catalysed C-H functionalisation. Additionally, his group is working on the synthesis and structure–activity relationship studies of anticancer and antibacterial natural products.

2. The reversible covalent bond for transition metal-catalysed C-H functionalisation

2.1 The C(sp^2)-H functionalisation of aldehydes

Aldehydes are incredibly important structural units in agrochemicals and pharmaceuticals and are key intermediates in chemical synthesis.[5] The C-H bond functionalisation of aldehydes enabled by transient ligands can install common and valuable functional groups for further manipulations. Among these reactions, the reversible installation of transient ligands to form corresponding imine directing groups can be used for C-H bond functionalisation of aldehydes.

The pioneering work in the field of C-H functionalisation with transient ligands was explored by the Jun group in 1997. They reported the first example of Rh(I)-catalysed aldehyde C-H bond activation by employing 2-amino-3-picoline (**L1**) as a transient ligand (Scheme 2a).[6a] Next, they updated their catalytic system to improve the efficiency and substrate scope. In this process, a catalytic amount of benzoic acid and anilines were proved to be effective additives as they accelerated the imine formation (Scheme 2b).[6b] Additionally, branched as well as linear α,β-unsaturated ketones could be produced from aldehydes and alkynes by a transient ligand-enabled hydroacylation process (Scheme 2c).[6c]

Subsequently, Breit and co-workers probed a bidentate transient ligand **L2**, 2-amino-3-picoline decorated with a phosphine at the C6 position, to increase the effective molarity, and thus realized the inter- and intra-molecular hydroacylation of alkenes, which avoided the use of any other additives and decreased the loading of the catalysts (Scheme 2d).[7] Moreover, Douglas group developed an intramolecular hydroacylation reaction to access 6- or 7- membered ring ketone synthesis using a 2-amino-3-picoline-based transient ligand. They also developed enantioselective hydroacylation utilizing a chiral ligand **L3** with moderate *ee* (Scheme 2e).[8]

Using the transient ligand directed strategy, both aldehyde C-H and aromatic bonds could be activated to form the cyclization products. In 2010, Takai *et al.* described Rh-catalysed synthesis of indenone derivatives from three equivalents benzaldehydes via a cycloaddition pathway using *N*-phenylacetamide (**L4**) as a transient ligand (Scheme 3a).[9] In 2013, the Seayad group reported a Rh(III)-amine dual catalysis for the oxidative coupling of aldehydes to form phthalide derivatives in the presence of a catalytic amount of 4-trifluoromethyl aniline (**L5**) (Scheme 3b).[10] Furthermore, with cheap anthranilic acid (**L6**), the first synthesis of fluorenones from benzaldehydes and aryl iodides has been reached by the Sorensen group (Scheme 3c).[11]

Recently, the Cheng group reported a Rh(III)-catalysed bilateral cyclization of benzaldehydes with nitrosos to form acridien derivatives in the presence of a catalytic amount of BnNH$_2$ (**L7**) (Scheme 3d).[12a] Furthermore, Park and Kim group demonstrated that anthranils could be used as both transient ligands and amination sources to afford 2-acyl acridines through Rh-catalysed direct C−H amination and acid-mediated cyclization (Scheme 3e).[12b]

In recent years, different benzaldehydes have been investigated with various metal catalysts for C(sp^2)–H bond functionalisation reactions. In 2017, transient ligand (**L6**, **L8** or **L9**)−enabled Pd-catalysed C-H arylation, chlorination, and

bromination of benzaldehyde substrates were reported by the Yu and Zhang groups. In their studies, it was found that the concentration of acid additives and transient ligands played a vital role in the *ortho*-C(sp²)-H functionalisation of the benzaldehydes (Scheme 4a, 4b, and 4c).[13] Furthermore, the Sorensen group unveiled that the *o*-hydroxylation of benzaldehydes could be achieved using *p*-TsOH as the hydroxyl source and 2-amino-4-chlorobenzoic acid (**L10**) as the transient ligand (Scheme 4d).[14a] In 2018, they also found that 2-aminobenzenesulfonic acids (**L11-L12**) acting as the transient ligands could efficiently achieve *ortho*-fluorination and *ortho*-methylation of benzaldehydes with 1-fluoro-2,4,6-trimethylpyridinium triflate serving as the fluorine source and potassium methyl trifluoroborate serving as the methyl source (Scheme 4e and 4f).[14b]

ortho-C-H iridation intermediate was isolated to support the proposed reaction mechanism (Scheme 5a).[15] The Yu/Zhang and Chen/He groups independently developed Ir-catalysed *ortho*-amidation reactions with organic azides using electron poor anilines (**L14-L15**) as transient ligands (Scheme 5b and 5c).[16] In addition, using 4-trifluoromethylaniline (**L16**) as the transient ligand, Jiao and coworkers found that dioxazolone could be used as amide sources for the *ortho*-amidation of benzaldehydes in decent yields via decarboxylation and migratory insertion steps (Scheme 5d).[17] In 2017, Zhang and coworkers reported the ruthenium catalysed *ortho*-alkylation of benzaldehydes with maleimides using 2-methyl-3-(trifluoromethyl)aniline (**L17**) as a transient ligand (Scheme 5e). Later, they found that ruthenium was also a suitable catalyst for C-H amination of benzaldehydes with organic azides, using catalytic electron poor anthranilic acids and anilines (**L17-L18**) as transient ligands (Scheme 5f).[18]

Scheme 2. The aldehyde C-H bond functionalisation enabled by transient ligands
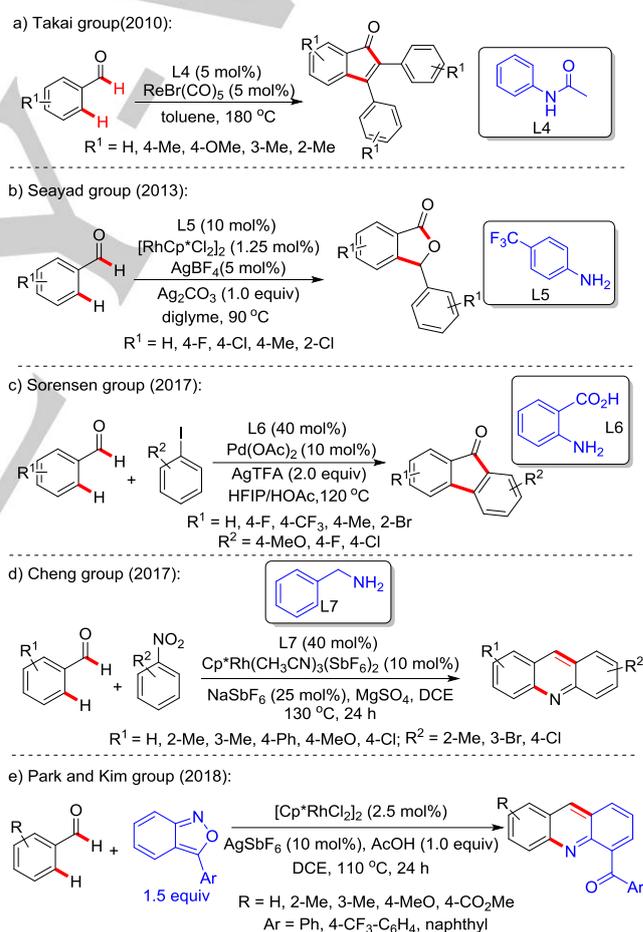
Scheme 3. Both aldehyde C-H and C(sp²)-H bond functionalisation enabled by transient ligands

Recently, Ir(III)-catalysed *ortho*-C-H alkylation of (hetero)aromatic aldehydes with alkyl boron reagents has been developed by the Sorensen group employing aniline (**L13**) as a transient ligand. An X-ray crystal structure of a benzaldehyde

Yu and Zhang group (2017):
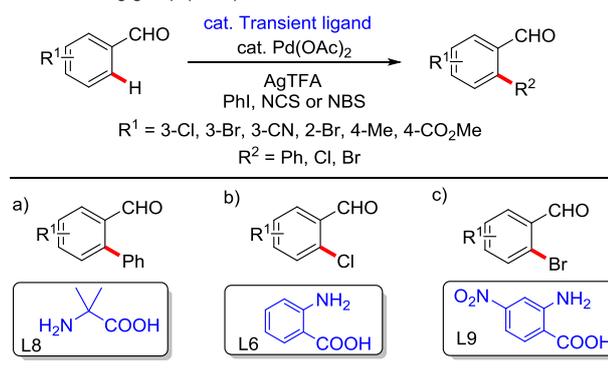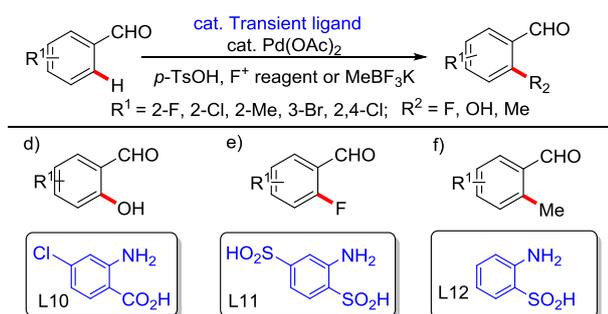
Scheme 4. Transient ligand-enabled Pd-catalysed C(sp²)-H functionalisation of aldehydes
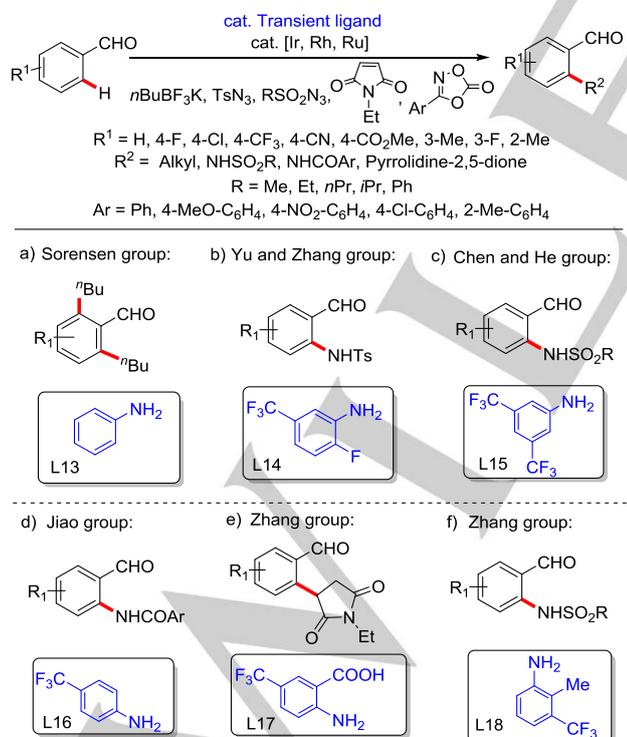
Scheme 5. Transient ligand-enabled Ir, Rh or Ru-catalysed C(sp²)-H functionalisation of aldehydes

In 2018, our group presented the first example of Pd-catalysed C-H bond arylation of five-membered heterocyclic aldehydes with 3-amino-3-methylbutanoic acid (L19) as a transient ligand. This strategy provided an opportunity to rapidly build up new mechanofluochromic materials. Through facile functional group modifications, we realized a novel synthetic strategy for mechanochromic luminogens with chromism trends of red- and blue-shift based on TPA-containing β-aryl-substituted five-membered heterocyclic carbonyl compounds (Scheme 6a).[19] A plausible reaction mechanism was also depicted in Scheme 6b. Condensation of 1 with L19 forms the imine intermediates I, which coordinates with palladium species to afford the corresponding six-membered cyclic palladium complex II. Then cyclo-metalation of II forms the intermediate III via a site-selective C-H bond activation process. Palladium (IV) complex IV is generated via the oxidative addition of III with an aryl iodide. Finally, reductive elimination of IV followed by the ligand dissociation and iodide abstracted by silver salts gives the intermediates VI, which releases the desired product 2 and regenerates the L19 (Scheme 6b).
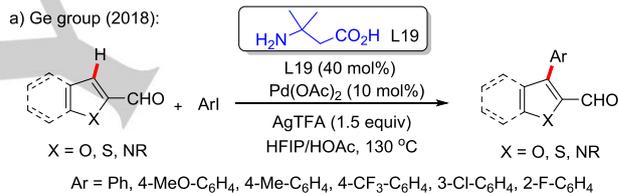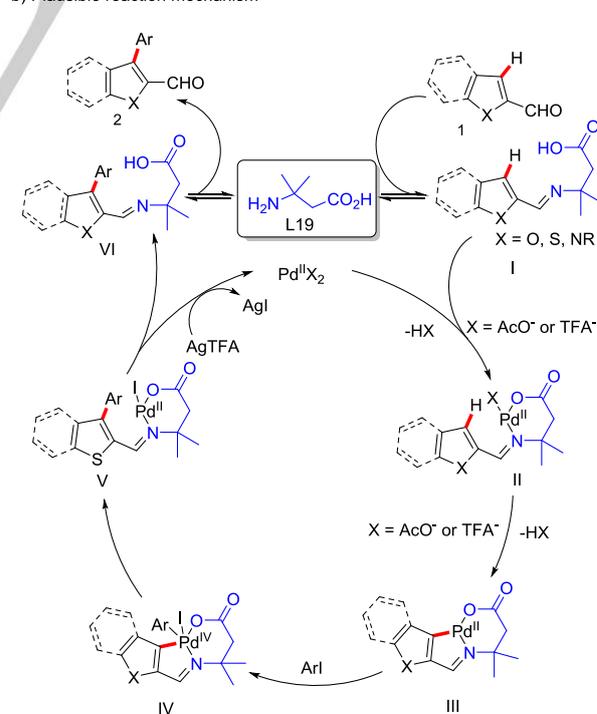
Scheme 6. Pd-catalysed C-H bond arylation of five-membered heterocyclic aldehydes with 3-amino-3-methylbutanoic acid as a transient ligand

Recently, Shi group demonstrated an efficient and practical strategy for the synthesis of axially chiral biaryls through Pd-catalysed atroposelective C-H olefination by employing commercially available l-*tert*-leucine (**L20**) as a transient ligand (Scheme 7a).[20a] Later, the same group also found that **L20** could be used for the atroposelective C-H alkynylation of biaryls with bromoalkynes (Scheme 7b).[20b] Very recently, Shi developed a Pd-catalysed atroposelective C-H allylation using **L20** as an efficient chiral transient ligand. In this work, various enantioenriched biaryls were obtained using this ligand with excellent enantioselectivities (up to 99% *ee*) (Scheme 7c and 7d).[20c]

In another study, Wang showed the first example of applying the transient strategy into the direct oxidative dehydrogenative arylation of aldehydes with arenes using 2-amino-2-methylpropanoic acid (**L8**) as a transient ligand. The cyclometallated intermediate was isolated and then treated under standard reaction conditions to form the product in 47% yield (Scheme 8).[21]

2.2. The benzylic C(sp³)-H functionalisation of aldehydes

The first example using a transient ligand for Pd(II)-catalysed C(sp³)–H bond functionalisation of aldehydes was reported by the Yu group in 2016.[22] Using glycine (**L21**) as a transient ligand, the arylation of C(sp³)–H bonds on 2-methylbenzaldehyde was achieved in good yields. In this reaction, water was added in order to reduce the concentration of the imine intermediates, which prevented their decomposition (Scheme 9a).[22] Furthermore, Pd(II)-catalysed enantioselective C-H arylation of *ortho*-alkylbenzaldehydes using a chiral amino acid was also demonstrated. The condition screening indicated that l-*tert*-leucine (**L20**) was the optimal transient ligand. Using this strategy, 2-ethyl-5-(trifluoromethyl)-benzaldehyde could be arylated with methyl 4-iodobenzoate to afford the desired product in 73% yield and 96% *ee* (Scheme 9b).

Very recently, the Yu group disclosed a Pd(II)-catalysed enantioselective C(sp³)-H fluorination using a catalytic amount of chiral ligand **L22**. In their work, a bulky amino amide ligand played a vital role in achieving high enantioselectivity and in promoting C-F reductive elimination (Scheme 9c).[23] Following those studies, the benzylic C(sp³)-H arylation of 2-methylbenzaldehyde was also achieved by Lei and Hu, which used acetohydrazide (**L23**) as the transient ligand (Scheme 9d).[24] Very recently, Jung and Kim demonstrated that an amino amide bearing a pendant hydroxyl group **L24** could also be used as the transient ligand for this process (Scheme 9e).[25a]

Very recently, Zhang showed an example of Pd-catalysed *ortho*-C(sp³)−H arylation of benzaldehydes with aryl diiodides through the transient ligand **L21** to construct the precursors of PAHs. The sequential intramolecular cationic cyclization and dehydration was demonstrated in the preparation of PAHs with good yields by employing TfOH as a Brønsted acid catalyst (Scheme 10).[25b]
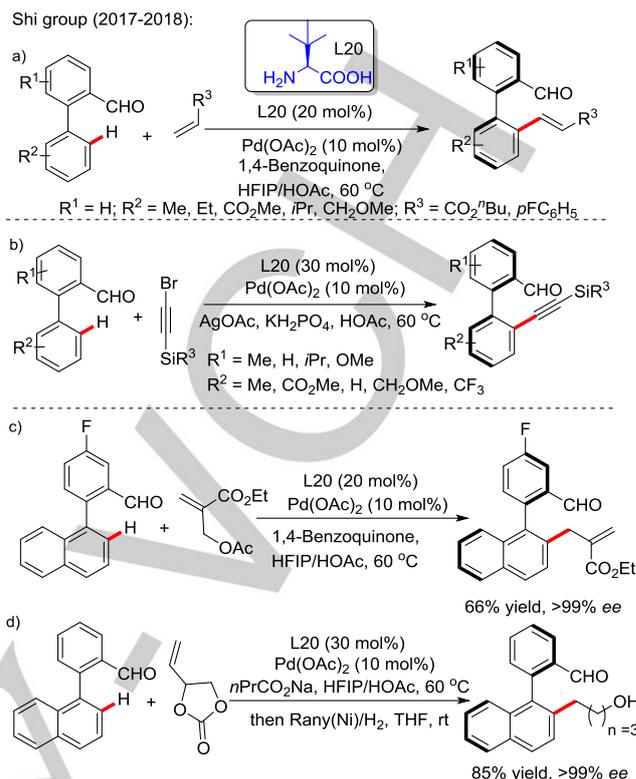
Scheme 7. The synthesis of axially chiral biaryls through transient ligand strategy

Scheme 8. The direct oxidative dehydrogenative arylation of aldehydes with arenes using 2-amino-2-methylpropanoic acid as a transient ligand

2.3. The C(sp³)-H functionalisation of aliphatic aldehydes

In 2016, our group reported the first example of Pd-catalysed direct arylation of unactivated β-C-H bonds of aliphatic aldehydes using either 3-aminopropanoic acid (**L25**) or 3-amino-3-methylbutanoic acid (**L19**) as the transient ligand.[26] In this work, the reaction condition screening study between 2-methylpentanal and iodobenzene indicated that 3-aminopropanoic acid was the optimal transient ligand (Scheme 11a). Next, the scope study of secondary aliphatic aldehydes showed that functionalisation of unactivated β-C(sp³)-H bonds of methyl groups was much more reactive than β-methylene and γ- or δ- terminal C-H bonds. Moreover, β-methylene C-H bonds of secondary aldehydes could also be arylated on both cyclic and β-branched substrates. It is noteworthy that unactivated β-C-H bonds of linear primary aliphatic aldehydes could also be

arylated with iodobenzene by employing 3-amino-3-methylbutanoic acid as the transient ligand (Scheme 11b). Additionally, it was found that this process had good functional group compatibility, and both electron-rich and electron-deficient aromatic rings could be efficiently incorporated into the aliphatic aldehydes in a highly site-selective manner.

a) Yu group (2016):

b) Yu group (2016):

C) Yu group (2018):

Other groups (2016, 2018):

d) Lei and Hu group (2016)

e) Jung and Kim group (2018)
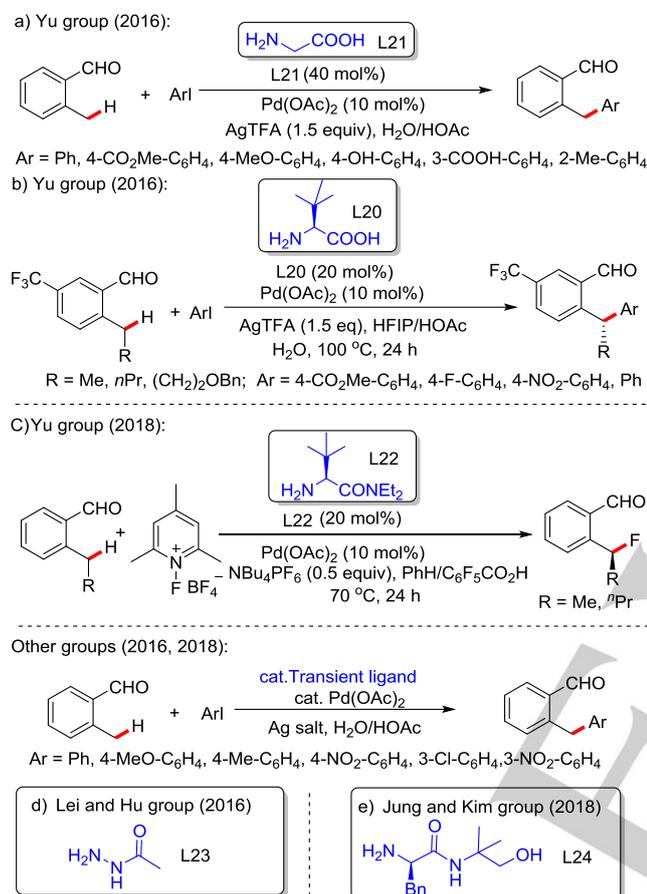
Scheme 9. The benzylic C(sp3)-H functionalisation of aldehydes

Zhang group (2018):
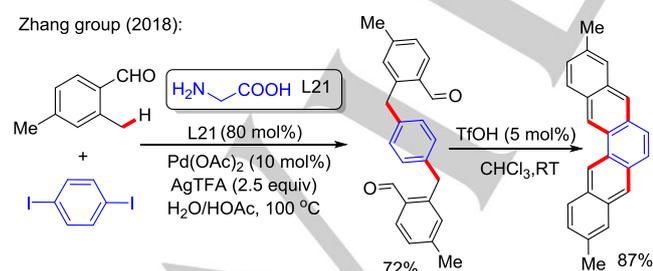
Scheme 10. Pd-catalysed *ortho*-C(sp3)−H arylation of benzaldehydes with aryl diiodides through the transient ligand to construct the precursors of PAHs

The mechanistic study showed that the [5,6]-bicyclic palladium intermediate could be isolated by using pyridine as an additional ligand. Furthermore, a series of control experiments were carried out and indicated that a sequential oxidation/addition process would not be involved in this reaction. A plausible reaction mechanism was also proposed. The condensation of aliphatic aldehyde with a transient ligand provides the aldimine **I**. Coordination of the aldimine **I** to the palladium specie produces the corresponding six-membered cyclic palladium complex **II**. Next, the cyclometallation takes place to give the [5,6]-bicyclic palladium intermediate **III** via a site-selective C-H bond activation process. Oxidative addition of the intermediate **III** with an aryl iodide generates the palladium species **IV**. Finally, reductive elimination of the palladium complex **IV** followed by the ligand dissociation and iodide abstraction processes gives the imine compound **VI**, which produces the desired product and releases a transient ligand (Scheme 11c). [26]

In 2017, Bull and coworkers demonstrated Pd-catalysed *β*-arylation of tertiary aliphatic aldehydes employing *N*-tosylethylenediamine (**L26**) as the transient ligand (Scheme 12a). The mechanistic studies showed that an unsymmetrical dimeric bicyclic palladium intermediate **Pd-dimer** could be prepared in acetonitrile, and its configuration was characterized by X-ray single crystal diffraction. The further insight experiments demonstrated that the **Pd-monomer** was formed when **Pd-dimer** dissolved in AcOD-*d4*, suggesting that monomeric species would be dominant under the reaction conditions (Scheme 12b).[27]

2.4. The C(sp2)-H functionalisation of ketones

Compared with aldehydes, the functionalisation of ketones using a transient ligand has several challenges: Firstly, the formation or hydrolysis of ketimine is less favored than the corresponding aldimine. Secondly, one of the ketimine E/Z isomer may have an inactive geometry for C-H functionalisation. Thirdly, the tautomerization between imine and enamine exists.

The Jun group was the first to release the Rh(I)-catalysed 2-alkylation of aryl ketones with olefins using benzylamine (**L7**) as a transient ligand. The mechanistic studies indicated that the key step of this process was the formation of a stable five-membered metallacycle (Scheme 13a).[28] A plausible reaction mechanism was also depicted in Scheme 13 b. The catalytic cycle starts with dissociation of PPh3 to form Rh complex **2**. Then the acetophenone reacts with benzylamine (**L7**) to form ketimine **1**, which coordinates with the Rh complex **2** to yield intermediate **3** followed by oxidative addition with the C-H bond to give the Rh-hydride product **4**. Then the intermediate **4** undergoes ligand exchange with an olefin hydride migratory insertion followed by reductive elimination to yield the alkylated ketimine **7**, which releases the final product under acidic reaction conditions (Scheme 13b). In 2006, the Takai group found that *p*-anisidine (**L27**) could also be used as a transient ligand for the rhenium-catalysed sequential addition and cyclization process through C-H bond activation in the reaction of aryl ketones with olefins (Scheme 13c).[29]

a) Ge group (2016):
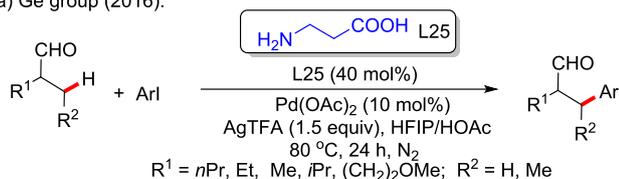
b)
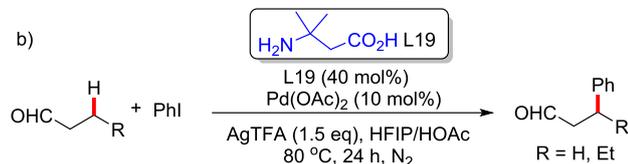
c) Plausible reaction mechanism
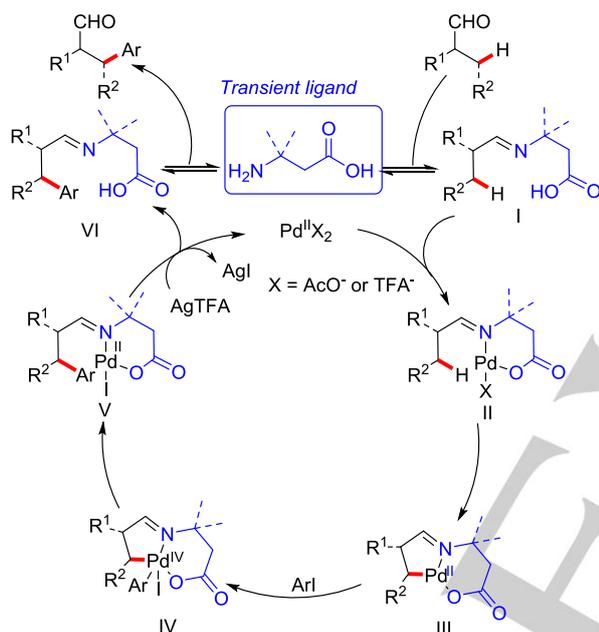
Scheme 11. The C(sp³)-H arylation of primary and secondary aliphatic aldehydes

a) Bull group (2017):
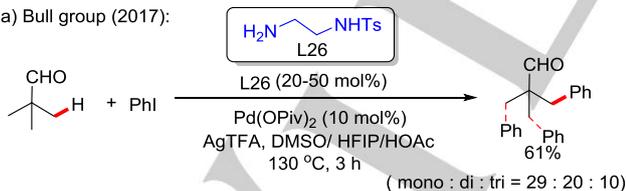
b) Mechansim study:
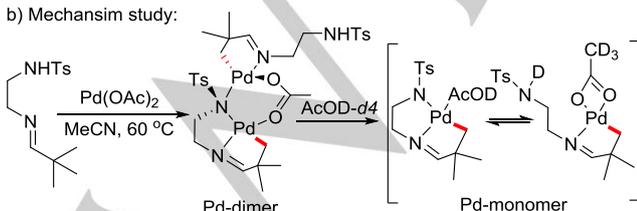
Scheme 12. The C(sp³)-H arylation of tertiary aliphatic aldehydes

a) Jun group (2002):
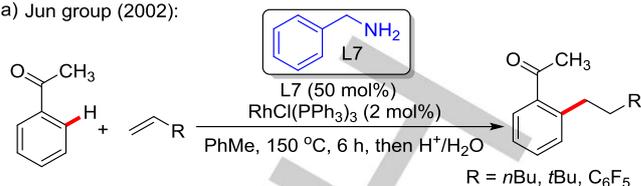
b) Plausible reaction mechanism
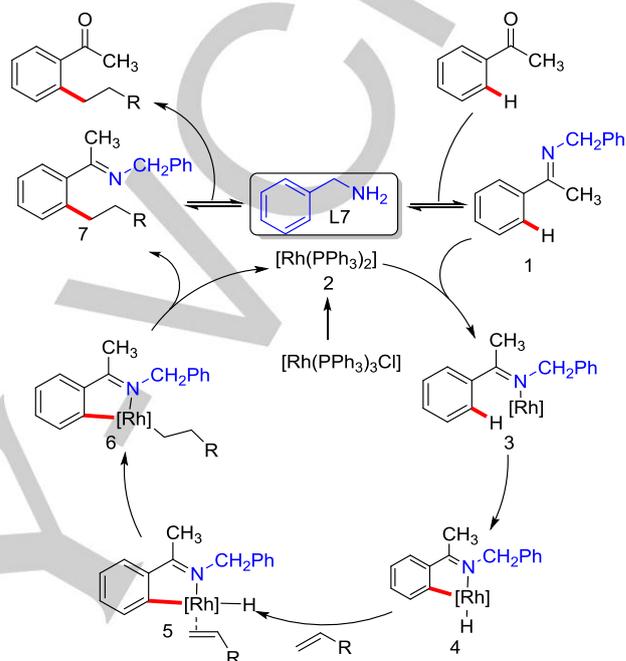
c) Takai group (2006):

Scheme 13. The C(sp²)-H arylation of aromatic ketones under Rh or Re catalyst

Inspired by Yu's work, the Xu and Jin group discovered the Pd(II)-catalysed direct C(sp²)-H arylation of aryl ketones with iodobenzene by employing the natural amino acid glycine (**L21**) as a transient ligand (Scheme 14a).[30a] In the same year, this group also developed the palladium-catalysed enantioselective 2-arylation reaction of ferrocenyl ketones through utilizing a catalytic amount of l-*tert*-leucine (**L20**) as a chiral transient ligand. The transformation was applied to the synthesis of different novel ferrocenyl-phosphine ligands with a special planar and stereogenic central chirality (Scheme 14b).[30b]

In 2018, our group demonstrated the palladium-catalysed direct arylation of heterocyclic aromatic ketones via a transient-ligand-directed strategy. We found that either 3-amino-3-methylbutanoic acid (**L19**) or glycine (**L21**) could be used as a

transient ligand to promote the direct C(sp²)-H functionalisation (Scheme 14c).[19]

Very recently, Lin and Wei group also demonstrated that a direct arylation of aromatic ketones was carried out through Pd-catalysed inert C(sp²)-H bond functionalisation with 2-amino-*N*-isopropyl-acetamide (**L28**) as a novel transient ligand. In this work, *α*-amino amide forming *N,N*-bidentate Pd-intermediate was much more favorable for the *β*-C(sp²)-H arylation of aromatic ketones under relatively mild conditions (Scheme 14d).[31a]
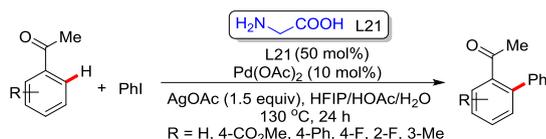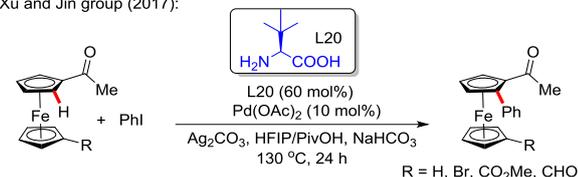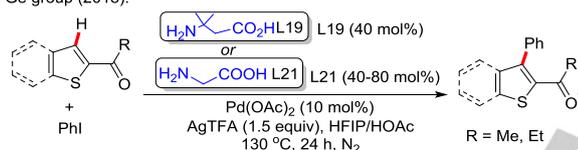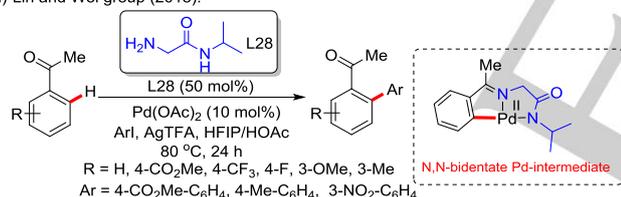
Scheme 14. The C(sp²)-H arylation of aromatic ketones

2.5. The C(sp³)-H functionalisation of ketones

In 2016, the Yu group elaborated the first example of Pd(II)-catalysed *β*-arylation of unactivated aliphatic ketones with glycine (**L21**) as a transient ligand (Scheme 15a).[22] In this work, *β*-C(sp³)-H bonds of methyl groups on linear, branched, and cyclic ketones were arylated with various aryl iodides. Furthermore, methylene C-H bonds on cyclic ketones could be activated. It should be noted that neither methylene C-H bonds on linear or branched ketones nor aliphatic aldehydes were tolerated by using glycine as a transient ligand. In 2018, Yu and co-workers found a modified *β*-amino acid **L29** (3-amino-2-benzylpropanoic acid) as the transient ligand that could enable Pd(II)-catalysed methylene *β*-C(sp³)-H arylation of linear aliphatic ketones (Scheme 15b).[31b]

Meanwhile, our group also demonstrated the Pd(II)-catalysed direct arylation of *β*-C(sp³)–H bonds in aliphatic ketones with cheap and commercially available *β*-alanine (**L25**) as the transient ligand (Scheme 16a). The ligand screening indicated that substitutions at the *α*-position of *β*-amino acid resulted in reduced yields due to the less favourable ketimine formation. Furthermore, the investigation of substrate scope showed that different functionalities, including ethers and esters, were also tolerated on the linear ketone substrates and (hetero)aryl iodides bearing different functional groups underwent arylation smoothly to produce the desired products. Moreover, our strategy could also be used for the unsymmetric double C-H arylation of ketones. Two different aryl groups were consecutively installed to provide 4-phenyl-4-(*p*-tolyl)butan-2-one in 41% isolated yield by employing a transient ligand *β*-alanine (Scheme 16b).[32]

Furthermore, Lin and Wei also found Pd-catalysed direct inert C(sp³)-H bond functionalisation of aliphatic ketones using 2-amino-*N*-isopropyl-acetamide as a novel transient ligand via a *N,N*-bidentate Pd-intermediate (Scheme 17).[31a]
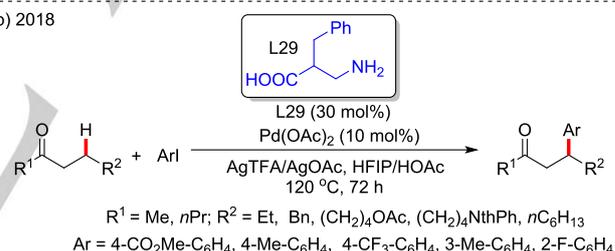
Scheme 15. The C(sp³)-H arylation of aliphatic ketones
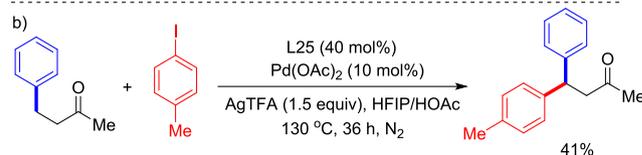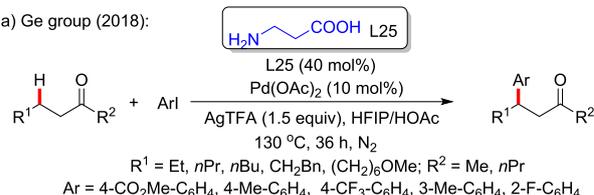
Scheme 16. The C(sp³)-H arylation of aliphatic ketones using *β*-alanine as a transient ligand

Lin and Wei group (2018):

R[1] = Me, Et, H; R[2] = Me, Et
R[3] = 4-CO$_2$Me, 4-CF$_3$, 4-F, 4-OMe, 4-Me
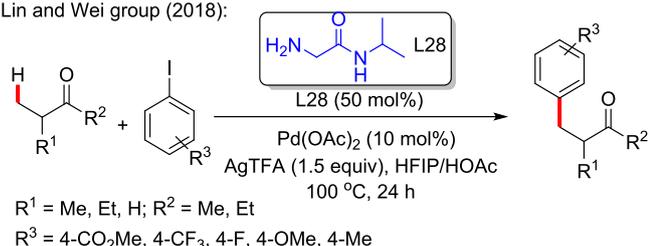
Scheme 17. The C(sp^3)-H arylation of aliphatic ketones using 2-amino-*N*-isopropyl-acetamide as the transient ligand

On the other hand, the formation of a reversible enamine could also be used in the functionalisation of ketones through the transient ligand strategy. In 2012, the Dong group reported the regioselective α-C-H bond alkylation of ketones with simple olefins using stoichiometric amounts of 2-aminopyridine (**L30**) as a ligand. This reaction proceeded through enamine C-H activation as the key step (Scheme 18a).[33] The proposed reaction mechanism was depicted in Scheme 18b. A cyclic 1,2-diketone **1** reacts with a stoichiometric amount of 2-aminopyridine (**L30**) to yield the corresponding enamine intermediate **2**. Then oxidative addition of Rh directed by pyridine provides Rh(III)-hydride species **3**. The intermediate **3** undergoes migratory insertion into the olefin to give the intermediate **4** followed by reductive elimination to generate *ortho*-alkylated product **5**, which then releases the final product **6** under acidic reaction conditions. To be mentioned, ligand **30** is recyclable in this process (Scheme 18b).

A) Dong Group (2012):
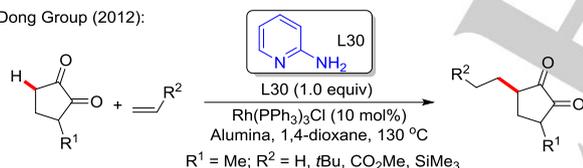
B) Plausible reaction mechanism
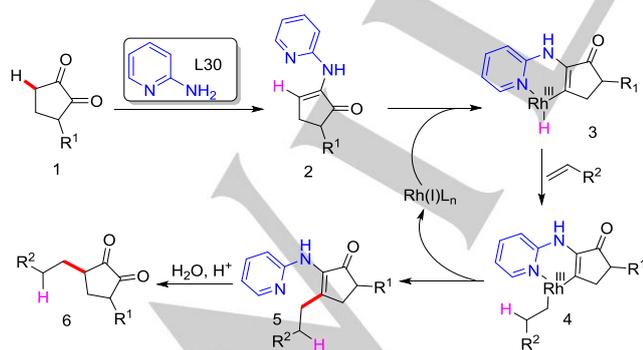
Scheme 18. The regioselective α-C-H bond alkylation of diketones with simple olefins using stoichiometric amounts of 2-aminopyridine

In 2014, the same group improved their catalytic system to decrease the amount of the ligand, using the 7-azaindoline (**L31**) as the most effective transient modifier. In this process, they introduced a novel ketone-alkylation strategy by employing the secondary amine and Rh(I) complexes catalyst to achieve C(sp^3)-H activation. Also, elegant alkylation of various simple ketones at the *alpha* position in good yield and selectivity was shown in this work. By using a catalytic acid, the secondary amine could be regenerated to achieve the catalytic cycle. The detailed control experiments showed that the key step is metal-H bond migratory insertion (Scheme 19a).[34] In 2015, the Dong group reported a bi-functional ligand **L31** enabled catalytic α-alkenylation of ketones with internal alkynes using a rhodium catalyst. In this process, both aromatic and aliphatic ketones were well tolerated and good yields were obtained. Both α,β- and β,γ-unsaturated ketones could be obtained by different workup reaction conditions — HCl in toluene or AcOH in CHCl$_3$, respectively (Scheme 19b).[35] In 2016, direct arylation of cyclopentanones with aryl bromides using transient ligand **L32** has been reported by the same group. This reaction has enabled by palladium and enamine cooperative catalysis (Scheme 19c).[36]

Dong Group
a) 2014

R[1] = Ph, CO$_2$Me, CH$_2$OH
R[2] = Ph, Me, SiMe$_3$, *t*Bu

b) 2015

R[1] = Ph, Me, Et, *n*Bu; R[2] = Ph, Me, Et, *n*Bu

c) 2016

85%
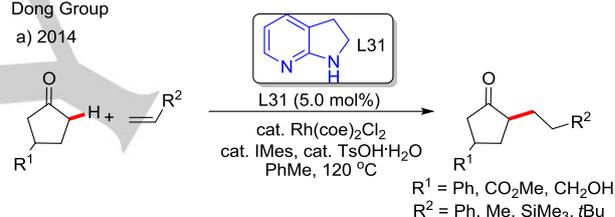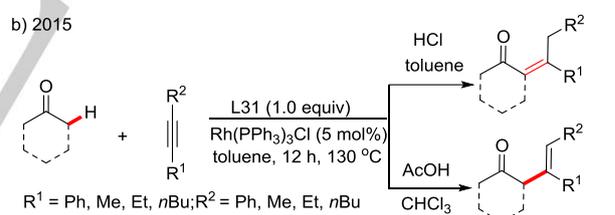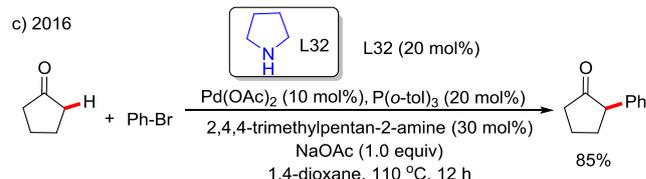
Scheme 19. Alkylation of simple ketones using reversibly enamine as the catalytic directing group

2.6. The C(sp^3)-H functionalisation of amines

Amines are ubiquitously in pharmaceuticals, agrochemicals, and biological chemicals with various biological activities.[37] Therefore, many medicines containing amine units are among the top selling drugs in the world.[38] Owing to their popularity and importance, efficient and straightforward strategies for the

synthesis of amine derivatives are always the focus of chemists' and pharmacists' studies.[39] Due to the reactivity and strong coordinating abilities of amines, functionalisation of free amines continues to be a synthetic challenge and still restricted to limited examples.[40]

Recently, several reactive transient ligands have been successfully applied to the γ-C(sp^3)-H arylation of free amines. In 2016, our group presented the palladium-catalysed direct γ-arylation of primary amines with catalytic glyoxylic acid monohydrate (**L33**) as a transient ligand (Scheme 20a).[41] It is worth mentioning that the arylation products were purified through acid/base workup without the need for chromatography. However, all amines needed a fully substituted α- or β-carbon for reactivity. In our study, a cyclopalladated complex has been isolated and characterised by X-ray crystallography in the presence of a stoichiometric amount of pyridine and palladium acetate (Scheme 20b).

The intermediate was further subjected to the standard reaction conditions to get the desired amine in 72% yield. Furthermore, a detailed reaction mechanism was proposed in Scheme 16. In the presence of acetic acid, a primary amine reacts with catalytic 2-oxoacetic acid to form the imine intermediate **I**. Coordination of this intermediate to the palladium species followed by a ligand exchange process produces palladium complex **II**. Cyclopalladation of intermediates **II** forms the five-membered ring intermediate **III**, and then oxidative addition of intermediate **III** with an aryl iodide yields the palladium(IV) species **IV**. Reductive elimination of this palladium complex followed by a ligand dissociation process provides α-imino acid **VI**, which then releases the final products, a process accelerated by the water molecule. During the process, AgTFA can probably abstract the iodides. Without Ag salts, this reaction could not proceed, which indicates that Ag salts play a vital role in the reaction (Scheme 20c). [41]

At the same time, Dong and coworkers independently reported the direct arylation of free amines using a stoichiometric amount of quinolone-8-carbaldehyde (**L34**) as an exo-imine-type transient ligand. Due to the volatility of some products, benzoylation is necessary for the isolation of the compound. Under the modified reaction conditions, C(sp^3)–H arylation of 2-*tert*-butylaniline derivatives was also demonstrated successfully (Scheme 21).[42]

Scheme 20. The C(sp^3)-H arylation of aliphatic amines using catalytic glyoxylic acid monohydrate as a transient ligand
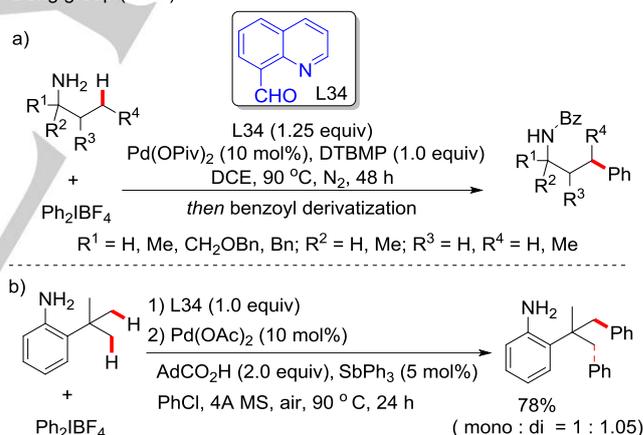
Scheme 21. The C(sp^3)-H arylation of aliphatic amines using quinolone-8-carbaldehyde as a transient ligand

Yu and coworkers revealed another highly reactive transient ligand for the γ-arylation of aliphatic free amines.[43] Notably, using commercially available 2-hydroxynicotinaldehyde (**L35**) as a ligand, this reaction system worked well with linear alkyl amines. A broad substrate scope was observed in this work with decent yields. Also, all products were derivatized by Boc-protection to aid isolation (Scheme 22a). Very recently, the δ-arylation of alkyl amines enabled by the combination of 2-(2-methoxyphenyl)-2-oxoacetic acid (**L36**) and pyridine derivatives has been reported by the Yu group. In this process, 5-substituted trifluoromethyl- and nitro-2-pyridone have been

identified as the optimal X-type ligands by acting as an internal base to accelerate the C-H bond cleavage step, which can significantly improve the efficiency of the δ-arylation of alkyl amines (Scheme 22b).[44] In 2016, the use of a stoichiometric amount of 3,5-di-*tert*-butylsalicylaldehyde (**L37**) as a precursor to form the removable and recoverable directing group for the γ-arylation of free primary amines has also been reported by Murakami and coworkers (Scheme 22c).[45]

In 2018, Kamenecka and coworkers reported Pd-catalysed γ-C(sp^3)-H and γ-C(sp^2)-H arylation of free amino esters using 2-hydroxynicotinaldehyde (**L35**).[46] It was found that the re-esterification is necessary for this reaction due to the hydrolysis of the ester (Scheme 23). Interestingly, Young group presented a strategy using a stoichiometric amount of dry ice to provide CO_2 as a ligand to mediate γ-arylation of aliphatic amines. It is assumed that a carbamate salt is the intermediate which undergoes an irreversible concerted metalation-deprotonation step to generate the key cyclopalladated intermediate (Scheme 24a and 24b).[47] Very recently, Bull and coworkers unveiled the use of a catalytic amount of stable alkyl acetal (**L38** or **L39**) as a transient ligand for the synthesis C(sp^3)-H arylation of primary amines. They uncovered an unexpected formation of a 7-membered palladacycle intermediate from activation of the ε-C(sp^2)-H bond (Scheme 24c).[48]

a) Yu group (2016):
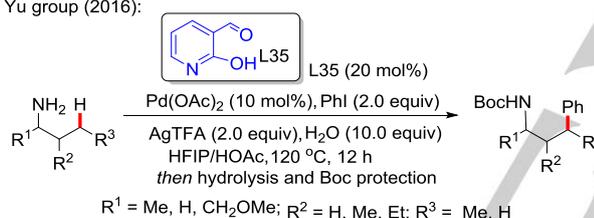
b) Yu group (2018):
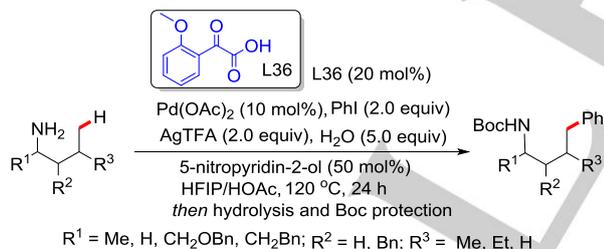
c) Murakami group (2016):
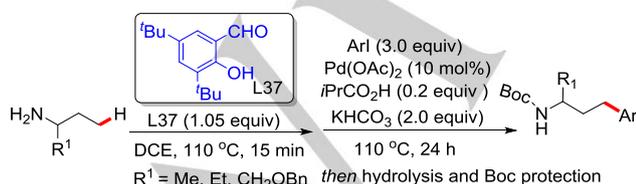
Scheme 22. The C(sp^3)-H γ-,δ-arylation of aliphatic amines

Kamenecka group (2018):
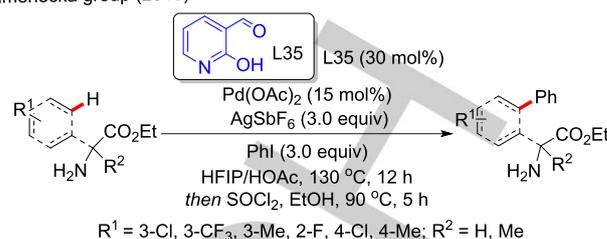
Scheme 23. Pd-catalysed γ-C(sp^3)-H and γ-C(sp^2)-H arylation of free amino esters using 2-hydroxynicotinaldehyde

Young group (2018):
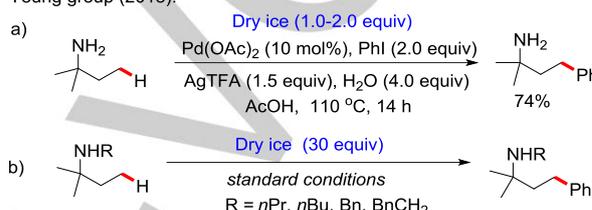
c) Bull group (2018):
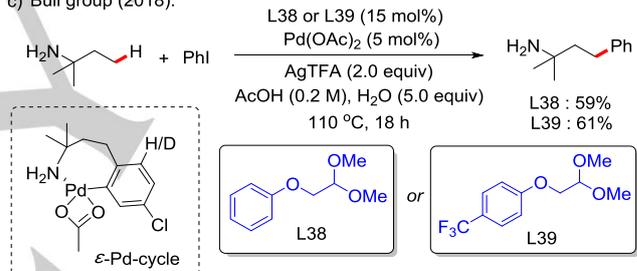
Scheme 24. The C(sp^3)-H γ--arylation of aliphatic amines using dry ice or alkyl aceta as transient ligands

2.7. The C-H functionalisation of phenols

In 2003, the Bedford group was the first to develop the *ortho*-selective C-H functionalisation of phenol derivatives using a [RhCl(PPh$_3$)$_3$]/P*t*Bu$_2$(OPh) system.[49] Unfortunately, this reaction had a limited substrate scope and was only suitable for *ortho*-substituted phenols (Scheme 25a). The proposed reaction mechanism was depicted in Scheme 25B. At first, in the presence of caesium carbonate, phenol derivative **1** reacts with **L40** to afford Compound **2**, then coordinates to orthometalates at a Rh complex **B,** with oxidative addition of the aryl halide from Rh **A** in the previous step, to from intermediate **3**. Subsequent reductive elimination of **3** followed by the ligand dissociation and reformation of the active catalyst to afford the final product **6** (Scheme 25b).

a) Bedford group (2003):

Ar = Ph, 4-Br-C$_6$H$_4$, 4-Me-C$_6$H$_4$, 4-MeO-C$_6$H$_4$, 4-MeCO-C$_6$H$_4$

b) Plausible reaction mechanism
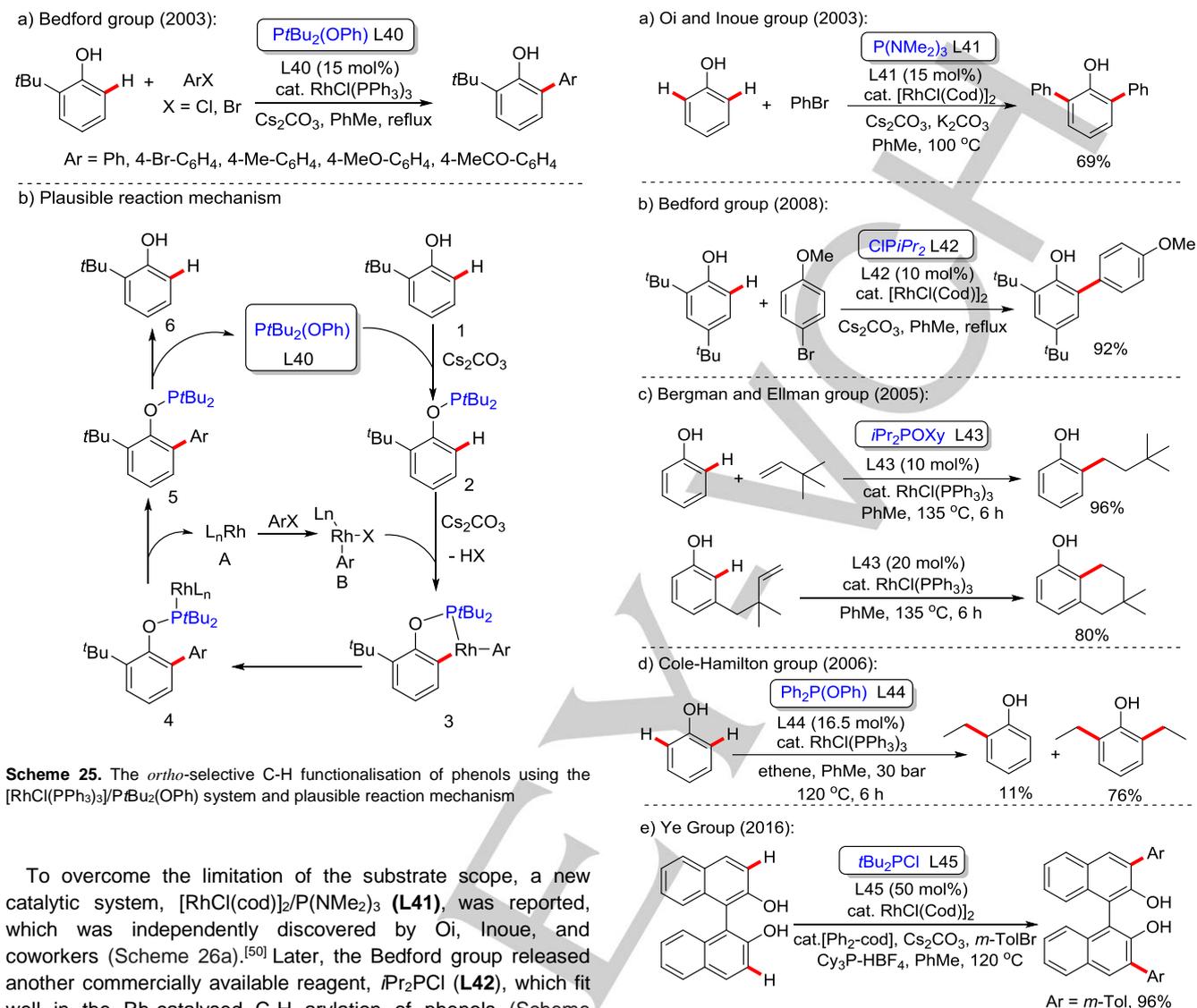
Scheme 25. The *ortho*-selective C-H functionalisation of phenols using the [RhCl(PPh$_3$)$_3$]/PtBu$_2$(OPh) system and plausible reaction mechanism

To overcome the limitation of the substrate scope, a new catalytic system, [RhCl(cod)]$_2$/P(NMe$_2$)$_3$ (**L41**), was reported, which was independently discovered by Oi, Inoue, and coworkers (Scheme 26a).[50] Later, the Bedford group released another commercially available reagent, iPr$_2$PCl (**L42**), which fit well in the Rh-catalysed C-H arylation of phenols (Scheme 26b).[51]

In 2005, inter- and intramolecular *ortho*-selective alkylation reactions of phenol derivatives with unactivated alkenes were reported by the Bergman and Ellman group using a RhCl(PPh$_3$)$_3$/iPr$_2$POXy (**L43**) system (Scheme 26c).[52] Later, the Cole-Hamilton group showcased a *ortho*-selective ethylation of phenol derivatives using a rhodium catalyst in the presence of a catalytic amount of Ph$_2$P(OPh) (**L44**) (Scheme 26d).[53] In 2016, the Ye group utilized this strategy to design an efficient way to access 3,3'-diaryl BINOLs by C-H bond arylation of 1,1'-bi-2-naphthol with aryl bromides. This straightforward synthetic approach provided the shortest route to the synthesis of 3,3'-diaryl BINOLs facilitated by a new ligand system, [Rh(cod)Cl]$_2$/tBu$_2$PCl (**L45**), Ph$_2$-cod and Cy$_3$P · HBF$_4$ (Scheme 26e).[54]

a) Oi and Inoue group (2003):

b) Bedford group (2008):

c) Bergman and Ellman group (2005):

d) Cole-Hamilton group (2006):

e) Ye Group (2016):

Ar = *m*-Tol, 96%

Scheme 26. The C-H functionalisation of phenols

3. Transition metal-catalysed C-H functionalisation via reversible non-covalent bond formation

3.1. Hydrogen-bonding-directed C-H functionalisation

Transition metal-catalysed C-H functionalisation via the formation of a hydrogen bond was reported by the Crabtree and Brudvig group in 2006. Using **L46**, which consisted of a di-*m*-oxo dimanganese core, 4-([2,2':6',2''-terpyridin]-4'-yl)aniline, and Kemp's triacid, Mn-catalysed selective oxygenation of an sp^3 C-H bond was realized due to non-covalent molecular recognition via hydrogen bonding between the carboxylic acid group of the catalyst and the carboxylic acid group of the substrate (Scheme 27).[55]

Crabtree and Brudvig group (2006):
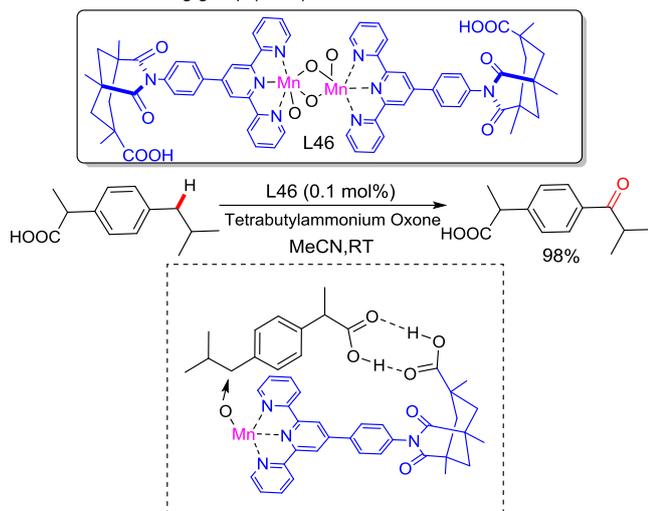
Scheme 27. Mn-catalysed selective C-H oxidation of sp^3 carbon atoms

a) Kanai and Kuninobu group (2015):

Scheme 28. A *meta*-selective borylation directed through hydrogen bonding between substrate and transient ligand

In 2015, the Kanai and Kuninobu group described a new approach for the *meta*-selective borylation of aromatic compounds with catalytic transient ligand **L47** (Scheme 28a). While avoiding the covalent auxiliary group formation, the secondary interaction between aromatic substrates and the designed catalyst controls the excellent *meta*-selectivity of C-H bond transformation. These novel ligands, acting as the reversible directing group, contain a bipyridine unit and pendant urea moiety. The pendant urea coordinates to the carbonyl group in the substrate through hydrogen bonding, which allows for the Ir(I)-catalysed *meta*-selective borylation of aromatic carbonyl compounds (aromatic amides, esters, phosphonates and phosphine oxides), in good yields and excellent *meta*-position selectivity under mild conditions. To be mentioned, this reversible hydrogen-bonding mode was confirmed by the H-NMR spectroscopy and control experiments (Scheme 28b).[56]

In 2017, *meta*-selective C-H borylation of common amine-containing aromatic molecules was reported by the Phipps group utilizing the ligand **L48** (Scheme 28c). In this work, the same ligand **L48** was proved to act as a hydrogen-bond acceptor to direct the *meta*-selective borylation of the aromatic substrates, in which the amide functionality acts as a hydrogen-bond donor (Scheme 28d).[57]

3.2. Transition metal-catalysed C-H functionalisation via the reversible ionic bond formation

The C-H functionalisation employing ion-pairing interactions was first released by Breslow and co-workers in 1981 (Scheme 29a).[58] Later, they described a single ion-pairing interaction approach enabled by radical relay chlorination to realize selective functionalisation of steroids. Although the selectivity and efficiency of this reaction was not satisfactory, this work provides an insight for the development of ion-pairing directed reactions (Scheme 29b).[59]

Recently, the Phipps group reported a fantastic strategy for achieving the Ir-catalysed *meta*-selective borylation of two distinct classes of aromatic quaternary ammonium salts by designing a suitable ion-pairing ligand. In this study, they assumed that readily accessed quaternary ammonium moiety present in the substrate would participate in the ion-pairing interactions with an anionic bifunctional ligand. Based on the calculation by Singleton, Maleczka, and Smith et al.,[60-61] Phipps and co-workers designed and modified the ligand to append a sulfonate-bearing tether onto the bipyridine back-bone. With the anionic ligand **48**, good to excellent *meta*-borylation of these compounds was obtained (up to 20:1). Control experiments in which the positive quaternary ammonium group is replaced by a neutral dimethylamine or *tert*-butyl group have shown no *meta* to *para* regioselectivity, supporting the ion pairing direction hypothesis.[62] However, these substrates possess very low conformational freedom. Later, it was found that in the presence of the same ligand (**L48**), more flexible quaternized phenethylamines and phenyl-propylamines were tolerated well under ion-pair directed borylation with good to excellent selectivity. In addition, competition between ion-pair and
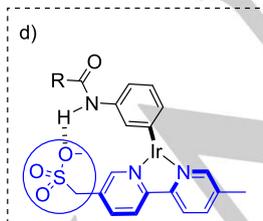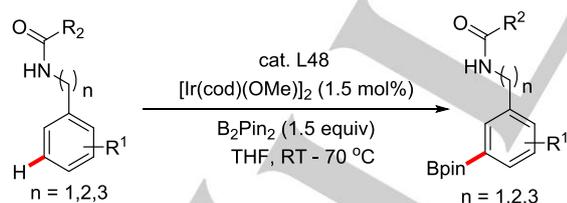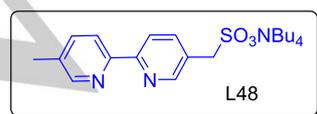
hydrogen bond direction was the investigated in specially designed substrates, showing that the ion pair-directed mode dominates to give highly selective borylation product (Scheme 29c). [63]

a) Breslow group (1981):

Ratio of alkylation at C5:C4 = 3.4:1

b) Breslow group (1983):

Ratio of Chlorination at C9:C14 = 3.5:1

c) Phipps group (2016, 2018):

n=1,2,3

d)

R = 2-Cl, 2-Br, 2-I, 2-CF$_3$, 2-F
2-CO$_2$Me, 2-Et, 3-F, 2,5-F$_2$

L48
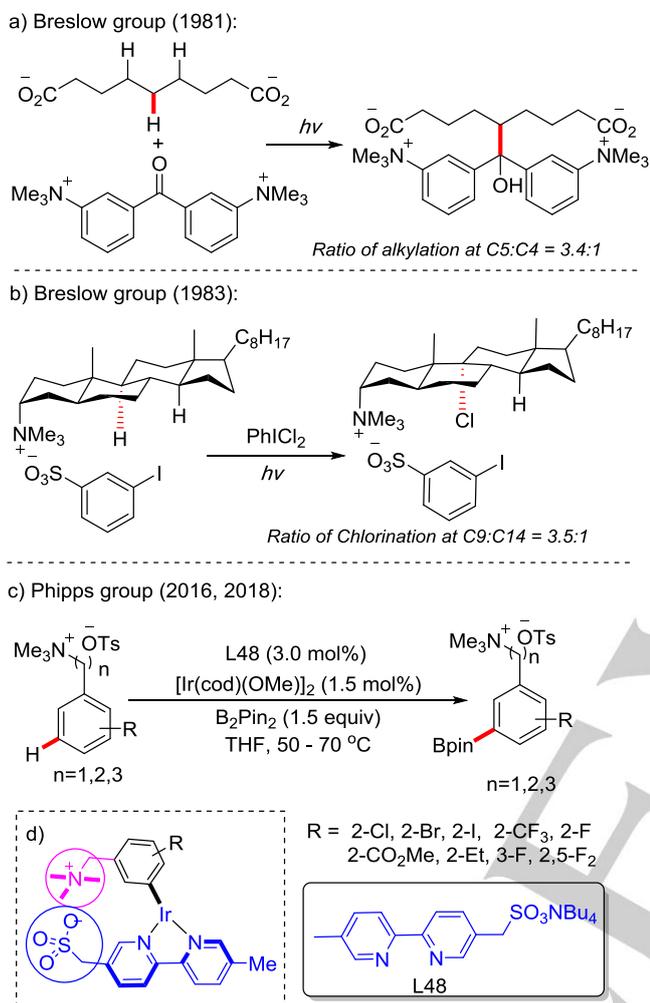
Scheme 29. Ion pair-directed C-H functionlisation

In 2017, the Chattopadhyay's group developed the first example of the *para*-selective borylation of aromatic esters enabled by non-covalent interactions between the L-shaped ligand **L49** and an iridium catalyst. Ligand **L49** is a simple bipyridine derivative with a quinolone unit, which would tautomerize into its more-stable quinolone form (Scheme 30a). In the presence of an Ir-catalyst and boron-reagent, the bipyridine part would generate a standard tris(boryl)iridium complex, and then the OH or O-M group would recognize the carbonyl oxygen through the non-covalent interaction, which would facilitate the *para* C-H activation of the ester derivatives (Scheme 30b).[64] In 2018, the Chattopadhyay's group released another example of the *meta*-selective borylation of aromatic amides in the presence of the same ligand and iridium catalyst. The substrate where the amide CO group is absent was initiated

in the standard reaction conditions, and it was found that borylation was non-selective (*meta* : other = 0.1:1). Notably, 3,5-disubstituted amide resulted in no borylation under the standard reaction condition (Scheme 30c).[65]

Chattopadhyay group:
a) 2017

R = 2-F, 2-Cl, 2-Me, 2-OMe, 2-CF$_3$, 2-CO$_2$Me, 2-Bn, 3-F, 2,5-F$_2$

b)

L49

c) 2018
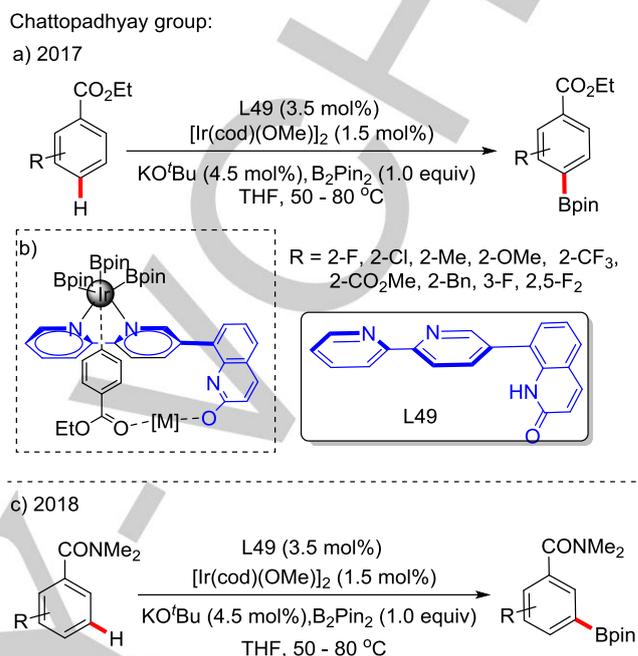
Scheme 30. L-shaped ligand directed Ir-catalysed *meta*-,*para*-C-H borylation.

4. Summary and Outlook

Novel transition-metal-catalysed selective C-H bond functionalisation strategies have been investigated and developed by scientists for many years. One such new strategy, which avoids the long-established pre-instillation and removal of directing groups, uses a transient ligand in a catalytic amount in order to convert a functional group into a directing group in a temporary and reversible fashion for C-H functionalisation reactions. Notably, the binding of the substrate-ligand complex, C-H functionalisation, and cleavage occurs in one reaction pot. Two major constraints in C-H functionalisation exist despite the recent advances: the use of certain functional groups (ketones, aldehydes, amines, phenols, etc.) and reaction types. However, in the future, it is expected that more progress and improvements will be made in regards to the type of reactions and the substrate scope.

Throughout this review, we have discussed transient ligand-enabled transition metal-catalysed C-H functionalisation strategies that use non-covalent and reversible covalent bonding methods. In our opinion, transient ligand-enabled transition metal-catalysed C-H functionalisation is a promising research area and will continue to garner more attention from scientists in the coming years.

Acknowledgements

Conflict of interest

The authors declare no conflict of interest

[1] a) X. Chen, K. M. Engle, D.-H, Wang, J.-Q. Yu, *Angew. Chem. Int. Ed.* **2009**, *48*, 5094-5115; *Angew. Chem.* **2009**, *121*, 5196-5217*;* b) L. Ackermann, *Chem. Rev.* **2011**, *111*, 1315–1345; c) T. W. Lyons, M. S. Sanford, *Chem. Rev.* **2010**, *110*, 1147–1169; d) M. C. Willis, *Chem. Rev.* **2010**, *110*, 725–748; e) G. E. Dobereiner, R. H. Crabtree, *Chem. Rev.* **2010**, *110*, 681–703; f) G. Rouquet, N. Chatani, *Angew. Chem. Int. Ed.* **2013**, *52*, 11726-11743*; Angew. Chem.* **2013**, *125,* 11942-11959; g) Y. Park, Y. Kim, S. Chang, *Chem. Rev.* **2017**, *117*, 9247–9301; h) Z, Dong, Z, Ren, S. J. Thompson, Y, Xu, G.-B. Dong, *Chem. Rev.* **2017**, *117*, 9333–9403.

[2] a) G. Chen, W. Gong, Z, Zhuang, M. S. Andrä, Y.-Q, Chen, X. Hong, Y.-F. Yang, T. Liu, K. N. Houk, J.-Q. Yu, *Science* **2016**, *353*, 1023-1027; b) R.-H. Mei, J. Loup, L. Ackermann, *ACS Catal.* **2016**, *6*, 793-797; c) Q.-Q. Lu, S. V.Céspedes, T. Gensch, F. Glorius, *ACS Catal.* **2016**, *6*, 2352-2356; d) Z.-K. Chen, B.-J. Wang, J.-T. Zhang, W.-L. Yu, Z.-X. Liu, Y.-H. Zhang, *Org. Chem. Front.* **2015**, *2*, 1107-1295; e) Y.-B. Liu, K. Yang, H.-B. Ge, *Chem. Sci.* **2016**, *7*, 2804-2808; f) V. G. Zaitsev, D. Shabashov, O. Daugulis, *J. Am. Chem. Soc.* **2005**, *127*, 13154-13155; g) Y. Aihara, N. Chatani, *J. Am. Chem. Soc.* **2013**, *135*, 5308-5311; h) D. shabashov, O. Daugulis; *J. Am. Chem. Soc.* **2010**, *132*, 3965-3972; i) Z. Ren, F.-Y. Mo, G.-B. Dong, *J. Am. Chem. Soc.* **2012**, *134*, 16991-16994; j) Y.-Y. Yang, X.-D. Qiu, Y. Zhao, Y.-C. Mu, Z.-Z. Shi, *J. Am. Chem. Soc.* **2016**, *138*, 495-498; k) H. Jiang, J. He, T. Liu, J.-Q. Yu, *J. Am. Chem. Soc.* **2016**, *138*, 2055-2059; l) J. He, Q. Shao, Q.-F. Wu, J.-Q. Yu, *J. Am. Chem. Soc.* **2017**, *139*, 3344-3347.

[3] W.-B. Ma, P. Gandeepan, J. Li, L. Ackermann, *Org. Chem. Front.* **2017**, *4*, 1435-1467.

[4] a) Q. Zhao, T. Polsson, X. Pannecouke, T. Besset, *Synthesis* **2017**, *49*, 4808-4826; b) P. Gandeepan, L. Ackermann, *Chem.* **2018**, *4*, 199-222; c) T. Bhattacharya, S. Pimparkar, D. Maiti, *RSC Adv.* **2018**, *8*, 19456-19464; d) S. St, J. Campbell, J. A. Bull, *Org. Biomol. Chem.* **2018**, *16*, 4582-4595.

[5] a) H. Y. Kim, P. J. Walsh, *Acc. Chem. Res.* **2012**, *45*, 1533-1547; b) L. V. R. Reddy, V. Kumar, R. Sagar, A. K. Shaw, *Chem. Rev.* **2013**, *113*, 3605–3631; c) A. Parenty, X. Moreau, J.-M. Campagne, *Chem. Rev.* **2006**, *106*, 911-939; d) K. Tatsuta, *J. Antibiot.* **2013**, *66*, 107-129; e) M. Y. Moskalik, B. A. Shainyan, U. Schilde, *Russ. J. Org. Chem.* **2011**, *47*, 1255-1260.

[6] a) C.-H. Jun, H. Lee, J.-B. Hong, *J. Org. Chem.* **1997**, *62*, 1200-1201; b) C.-H. Jun, D.-Y. Lee, H. Lee, J.-B. Hong, *Angew. Chem. Int. Ed.* **2000**, *39*, 3070-3072; *Angew. Chem.* **2000**, *112*, 3214-3216; c) C.-H. Jun, H. Lee, J.-B. Hong, B.-I. Kwon, *Angew. Chem. Int. Ed.* **2002**, *41*, 2146-2147; *Angew. Chem.* **2002**, *114*, 2250-2251.

[7] N. R. Vautravers, D. D. Regent, B. Briet, *Chem. Commun.* **2011**, *47*, 6635-6637.

[8] E. V. Beletskiy, C. Sudheer, C. J. Douglas, *J. Org. Chem.* **2012**, *77*, 5884-5893.

[9] Y. Kuninobu, T. Matsuki, K. Takai, *Org. Lett.* **2010**, *12*, 2948-2950.

[10] P.-W. Tan, N. A. B. Juwaini, J. Seayad, *Org. Lett.* **2013**, *15*, 5166-5169.

[11] X.-Y. Chen, S. Ozturk, E. J. Sorensen, *Org. Lett.* **2017**, *19*, 1140-1143.

[12] a) W.-M. Hu, Q.-H. Zheng, S. Sun, J. Cheng, *Chem. Commun.* **2017**, *53*, 6263-6266; b) S. Kim, S. H. Han, N. K. Mishra, R. Chun, Y. H. Jung, H. S. Kim, J. S. Park, I. S. Kim, *Org. Lett.* **2018**, *20*, 4010-4014.

[13] X.-H. Liu, H. Park, J.-H. Hu, Y. Hu, Q.-L. Zhang, B.-L. Wang, B. Sun, K.-S. Yeung, F.-L. Zhang, J.-Q. Yu, *J. Am. Chem. Soc.* **2017**, *139*, 888-896.

[14] a) X.-Y. Chen, S. Ozturk, E. J. Sorensen, *Org. Lett.* **2017**, *19*, 6280-6283; b) X.-Y. Chen, E. J. Sorensen, *J. Am. Chem. Soc.* **2018**, *140*, 2789-2792.

[15] X.-Y. Chen, E. J. Sorensen, *Chem. Sci.* **2018**, *9*, 8951-8956.

[16] a) D.-L. Mu, X.-M. Wang, G. Chen, G. He, *J. Org. Chem.* **2017**, *82*, 4497-4503; b) X.-H. Liu, H. Park, J.-H. Hu, Y. Hu, Q.-L. Zhang, B.-L. Wang, B. Sun, K.-S. Yeung, F.-L. Zhang, J.-Q. Yu, *J. Am. Chem. Soc.* **2017**, *139*, 888-896.

[17] X.-Y. Wang, S. Song, N. Jiao. *Chin. J. Chem.* **2018**, *36*, 213−216.

[18] a) F. Li, Y.-R. Zhou, H. Yang, D.-D. Liu, B. Sun, F.-L. Zhang, *Org. Lett.* **2018**, *20*, 146-149; b) O. K. Rasheed. *Synlett* **2018**, *29*, 1033-1036.

[19] B.-J. Li, K. Seth, B. Niu, L. Pan, H.-W. Yang, H.-B. Ge, *Angew. Chem. Int. Ed.* **2018**, *57*, 3401-3405; *Angew. Chem.* **2018**, *130*, 3459-3463.

[20] a) Q.J. Yao, S. Zhang, B.-B. Zhan, B.-F. Shi, *Angew. Chem. Int. Ed.* **2017**, *56*, 6617-6621; *Angew. Chem.* **2017**, *129*, 6717-6721; b) G. Liao, Q.-J. Yao, Z.-Z. Zhang, Y.-J. Wu, D.-Y. Huang, B.-F. Shi, *Angew. Chem. Int. Ed.* **2018**, *57*, 3661-3665; *Angew. Chem.* **2018**, *130*, 3723-3727; c) G. Liao, B. Li, H.-M. Chen, Q.–J. Yao, Y.-N. Xia, J. Luo, B.-F. Shi, *Angew. Chem. Int. Ed.* **2018**, *57*, 17151-17155; *Angew. Chem.* **2018**, *130*, 17397-17401.

[21] D.-Y. Wang, S.-H. Guo, G.-F. Pan, X.-Q. Zhu, Y.-R. Gao, Y.-Q. Wang, *Org. Lett.* **2018**, *20*, 1794-1797.

[22] F.-L. Zhang, K. Hong, T.-J. Li, H. Park, J.-Q. Yu, *Science* **2016**, *351*, 252-256.

[23] H. Park, P. Verma, K. Hong, J.-Q. Yu, *Nat. Chem.* **2018**, *10*, 755-762.

[24] F. Ma, F. Lei, L.-H. Hu, *Org. Lett.* **2016**, *18*, 2708-2711.

[25] a) H. Park, K. Yoo, B. Jung, M. Kim, *Tetrahedron* **2018**, *74*, 2048-2055; b) M. Tang, Q. Yu, Z. Wang, C. Zhang, B. Sun, Y. Yi, F.-L. Zhang, *Org. Lett.* **2018**, *20*, 7620-7623.

[26] K. Yang, Q. Li, Y.-B. Liu, G.-G. Li, H.-B. Ge, *J. Am. Chem. Soc.* **2016**, *138*, 12775-12778.

[27] S. S. J. Campbell, A. J. P. White, J. A. Bull, *Chem. Sci.* **2017**, *8*, 4840-4847.

[28] C.-H Jun, C. W. Moon, J.-B. Hong, S.-G. Lim, K.-Y. Chung, Y.-H. Kim, *Chem. Eur. J.* **2002**, *8*, 485-492.

[29] Y. Kuninobu, Y. Nishina, M. Shouho, K. Takai, *Angew. Chem. Int. Ed.* **2006**, *45*, 2766-2768; *Angew. Chem.* **2006**, *118*, 2832-2834.

[30] a) J.-C. Xu, Y. Liu, Y. Wang, Y.-J. Li, X.-H. Xu, Z. Jin, *Org. Lett.* **2017**, *19*, 1562-1565; b) J.-C. Xu, Y. Liu, J.-L. Zhang, X.-H. Xu, Z. Jin, *Chem. Commun.* **2018**, *54*, 689-692.

[31] a) J. Wang, C. Dong, L. Wu, M. Xu, J. Lin, K. Wei, *Adv. Synth. Catal.* **2018**, *360*, 3709-3715; b) K. Hong, H. Park, J.-Q. Yu, *ACS Catal.* **2017**, *7*, 6938-6941.

[32] L. Pan, K. Yang, G.-G. Li, H.-B. Ge, *Chem. Commun.* **2018**, *54*, 2759-2762.

[33] Z.-Q. Wang, B. J. Reinus, G.-B. Dong, *J. Am. Chem. Soc.* **2012**, *134*, 13954-13957.

[34] F.-Y. Mo, G.-B. Dong, *Science* **2014**, *345*, 68-72.

[35] F.-Y. Mo, H. N. Lim, G.-B. Dong, *J. Am. Chem. Soc.* **2015**, *137*, 15518-15527.

[36] Y. Xu, T.-S. Su, Z.-X. Huang, G.-B. Dong, *Angew. Chem. Int. Ed.* **2016**, *55*, 2559-2563; *Angew. Chem.* **2016**, *128*, 2605-2609.

[37]　a) T. P. T. Cushnie, B. Cushnie, A. J. Lamb, *Int. J. Antimicrob. Agents* **2014**, *44*, 377-386; b) P. Kittakoop, C. Mahidol, S. Ruchirawat, *Curr. Top. Med. Chem.* **2014**, *14*, 239-252.

[38]　a) E. Vitaku, D. T. Smith, J. T. Njardarson, *J. Med. Chem.* **2014**, *57*, 10257-10274; b) N. A. Mcgrath, M. Brichacek, J. T. Niardarson, *J. Chem. Educ.* **2010**, *87*, 1348-1349.

[39]　a) A. Hager, N. Vrielink, D. Hager, J. Lefranc, D. Trauner, *Nat. Prod. Rep.* **2016**, *33*, 491-522; b) R. N. Salvatore, C. H. Yoon, K. W. Jung, *Tetrahedron* **2001**, *57*, 7785-7811.

[40]　a) J. W. Beatty, C. R. J. Stephenson, *Acc. Chem. Res.* **2015**, *48*, 1474-1484; b) C.-J. Li, *Acc. Chem. Res.* **2009**, *42*, 335-344; c) S. A. Girard, T. Knauber, C.-J. Li, *Angew. Chem. Int. Ed.* **2014**, *53*, 74-100; *Angew. Chem.* **2014**, *126*, 76-103; d) C. He, M. J. Gaunt, *Angew. Chem. Int. Ed.* **2015**, *54*, 15480-15844; *Angew. Chem.* **2015**, *127*, 16066-16070; e) A. McNally, B. Haffemayer, B. S. L. Collins, M. J. Gaunt, *Nature* **2014**, *510*, 129-133; f) J. Calleja, D. Pla, T. W. Gorman, V. Domingo, B. Haffemayer, M. J. Gaunt, *Nat. Chem.* **2015**, *7*, 1009-1016; g) K. Chen, D. Wang, Z.-W. Li, Z. Liu, F. Pan, Y.-F. Zhang, Z.-J. Shi, *Org. Chem. Front.* **2017**, *4*, 2097-2101.

[41]　Y.-B. Liu, H.-B. Ge, *Nat.Chem.* **2017**, *9*, 26-32.

[42]　Y. Xu, M. C. Young, C.-P. Wang, D. M. Magness, G.-B. Dong, *Angew. Chem. Int. Ed.* **2016**, *55*, 9084-9087; *Angew. Chem.* **2016**, *128*, 9230-9233.

[43]　Y.-W. Wu, Y.-Q. Chen, T. Liu, M. D. Eastgate, J.-Q. Yu, *J. Am. Chem. Soc.* **2016**, *138*, 14554-14557.

[44]　Y.-Q. Chen, Z. Wang, Y.-W. Wu, S. R. Wisniewski, J. X. Qiao, W. R. Ewing, M. D. Eastgate, J.-Q. Yu, *J. Am. Chem. Soc.* **2018**, *140*, 17884-17894.

[45]　A. Yada, W.-Q. Liao, Y.Sato, M. Murakami, *Angew. Chem. Int. Ed.* **2017**, *56*, 1073-1076; *Angew. Chem.* **2017**, *129*, 1093-1096.

[46]　H. Lin, C. Wang, T. D. Bannister, T. M. Kamenecka, *Chem. Eur. J.* **2018**, *24*, 9535-9541.

[47]　M. Kapoor, D. Liu, M. C. Young, *J. Am. Chem. Soc.* **2018**, *140*, 6818-6822.

[48]　S.S. J. Campbell, A. K. Ou, J. A. Bull, *Chem. Eur. J.* **2018**, *24*, 17838-17843.

[49]　R. B. Bedford, S. J. Coles, M. B. Hursthouse, M. E. Limmert, *Angew. Chem. Int. Ed.* **2003**, *42*, 112-114; *Angew. Chem.* **2003**, *115*, 152-156.

[50]　S. Oi, S.-I. Watanabe, S. Fukita, Y. Inoue, *Tetrahedron Lett.* **2003**, *44*, 8665-8668.

[51]　R. B. Bedford, M. Betham, A. J. M. Caffyn, J. P. H. Charmant, L. C. L. Alleyne, P. D. Long, D. P. Cerón, S. Prashar, *Chem. Commun.* **2008**, 990-992.

[52]　J. C. Lewis, J. Wu, R. G. Bergman, J. A. Ellman, *Organometallics* **2005**, *24*, 5737-5746.

[53]　M. C. Carrón, D. J. C. Hamilton. *Chem. Commun.* **2006**, 4527-4529.

[54]　J.-F. Yang, R.-H. Wang, Y.-X. Wang, W.-W. Yao, Q.-S. Liu, M.-C. Ye, *Angew. Chem. Int. Ed.* **2016**, *55*, 14116-14120; *Angew. Chem.* **2016**, *128*, 14322-14326.

[55]　S. Das, C. D. Incarvito, R. H. Crabtree, G. W. Brudvig, *Science* **2006**, *312*, 1941-1943.

[56]　Y. Kuninobu, H. Ida, M. Nishi, M. Kanai, *Nat. Chem.* **2015**, *7*, 712-717.

[57]　H. J. Davis, G. R. Genov, R. J. Phipps, *Angew. Chem. Int. Ed.* **2017**, *56*, 13351-13355; *Angew. Chem.* **2017**, *129*, 13536-13540.

[58]　R. Breslow, R. Rajagopalan, J. Schwarz, *J. Am. Chem. Soc.* **1981**, *103*, 2905-2907.

[59]　R. Breslow, D. Heyer, *Tetrahedron. Lett.* **1983**, *24*, 5039-5042.

[60]　P. C. Roosen, V. A. Kallepalli, B. Chattopadhyay, D. A. Singleton, R. E. Maleczka Jr., M. R. Smith II, *J. Am. Chem. Soc.* **2012**, *134*, 11350-11353.

[61]　A. G. Green, P. Liu, C. A. Merlic, K. N. Houk, *J. Am. Chem. Soc.* **2014**, *136*, 4575-4583.

[62]　H. J. Davis, M. T. Mihai, R. J. Phipps, *J. Am. Chem. Soc.* **2016**, *138*, 12759-12762.

[63]　M. T. Mihai, H. J. Davis, G. R. Genov, R. J. Phipps, *ACS Catal.* **2018**, *8*, 3764-3769.

[64]　M. E. Hoque, R. Bisht, C. Haldar, B. Chattopadhyay, *J. Am. Chem. Soc.* **2017**, *139*, 7745-7748.

[65]　R. Bisht, M. E. Hoque, B. Chattopadhyay, *Angew. Chem. Int. Ed.* **2018**, *57*, 15762-15766; *Angew. Chem.* **2018**, *130*, 15988-15992.

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Transition metal-catalysed C–H functionlisation on sp^2 and sp^3 carbon centres with different transient working modes, including covalent bond, hydrogen and ionic bonds have been developed.
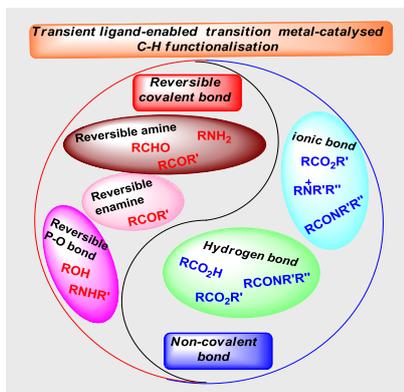
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Transient ligand-enabled transition metal-catalysed C-H functionlisation

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