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ARTICLE

Iridium-catalysed directed C–H functionalisation as a platform for stereoselective C–C bond formation

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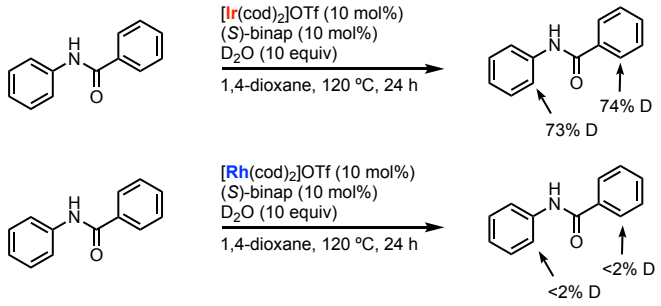
Transition-metal-catalysed direct C–H functionalisation has emerged as one of the most efficient molecular transformations, offering excellent atom and step economy. This methodology eliminates the need for pre-functionalisation of substrates, enabling the direct use of readily available starting materials, such as alkenes to access valuable compounds. In particular, enantioselective variants of these reactions have attracted considerable attention in recent years due to their utility in constructing complex molecules. In this context, iridium complexes have been effectively employed in enantioselective, atom- and step-economical transformations, enabling various types of C–H functionalisations, including hydroarylation and hydroalkylation. In this review, we summarise our recent studies on Ir-catalysed directing-group-assisted C–H bond addition to unsaturated bonds, together with related works from other research groups.

1. Introduction

The direct functionalisation of C–H bonds, which are ubiquitous in organic molecules, plays a pivotal role in modern organic synthesis. It enables the direct conversion of inert C–H bonds into various functional groups, thus eliminating the need for pre-functionalisation. This results in reduced waste, shorter synthetic routes and improved atom economy.[1] This approach is particularly useful for the rapid synthesis of diverse molecules in fields such as drug discovery and material science. A key strategy for this is transition-metal-catalysed C–H activation.[2] The addition of C–H bonds to unsaturated bonds, in particular, has attracted considerable attention in recent years, as it allows C–C bond formation with 100% atom economy. In addition, its enantioselective variants have also attracted increasing interest as they provide a rational approach to accessing a wide range of chiral molecules, such as benzylic stereocentres and heteroaromatic skeletons found in many natural products and pharmaceuticals.[3] Since the pioneering works of Lewis and Murai, who independently reported on the catalytic direct aromatic C–H bond addition to the olefins using the ruthenium catalysts, various transition metals have been applied to such transformations.[4,5]

Recently, iridium has been increasingly utilized for diverse catalytic C–H bond activation reactions, including alkylation, alkenylation, amidation, borylation, and silylation.[6] One distinctive feature of organoiridium complexes is the strength of their Ir–C and Ir–H bonds, which surpass those found in cobalt and rhodium analogues. This robust bonding plays a crucial role in the unique reactivity patterns of iridium catalysts.



Scheme 1. Deuterium incorporation experiments

For example, Nakai and co-workers reported that *ortho*-C–H activation in *N*-phenylbenzamide resulted in observable deuterium incorporation under a cationic iridium catalysis, but not when the rhodium complex was used instead (Scheme 1).[7] DFT studies attribute this difference to the significant relativistic effects present in heavier elements, which make iridacycles more stable than rhodacycles.[8] Regarding the reactivity of iridium(III)–carbon bonds, Wang, Xu, and co-workers reported that an aryliridium(III) species undergoes alkyne insertion more efficiently than the rhodium counterpart in the oxidative annulation of isoquinolones with alkynes, likely due to the higher electrophilicity of the iridium centre.[9]

The application of iridium complexes in effective catalytic systems has been designed to achieve high reaction efficiency as well as regio- and enantioselectivity.[10] Under these circumstances, our group has been actively engaged in the development of iridium-catalysed hydrocarbonation reactions *via* C–H bond activation, especially enantioselective reactions, for nearly a decade.[11] In this feature article, the developments

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in the iridium-catalysed C–H bond addition to unsaturated C–C multiple bonds, in particular, on the enantioselective reactions, including our contributions, are summarised.

2. Iridium-Catalysed Addition of C(sp^2)–H bonds

2-1. Intermolecular addition of C(sp^2)–H bonds to alkenes

Hydroarylation of bicycloalkenes

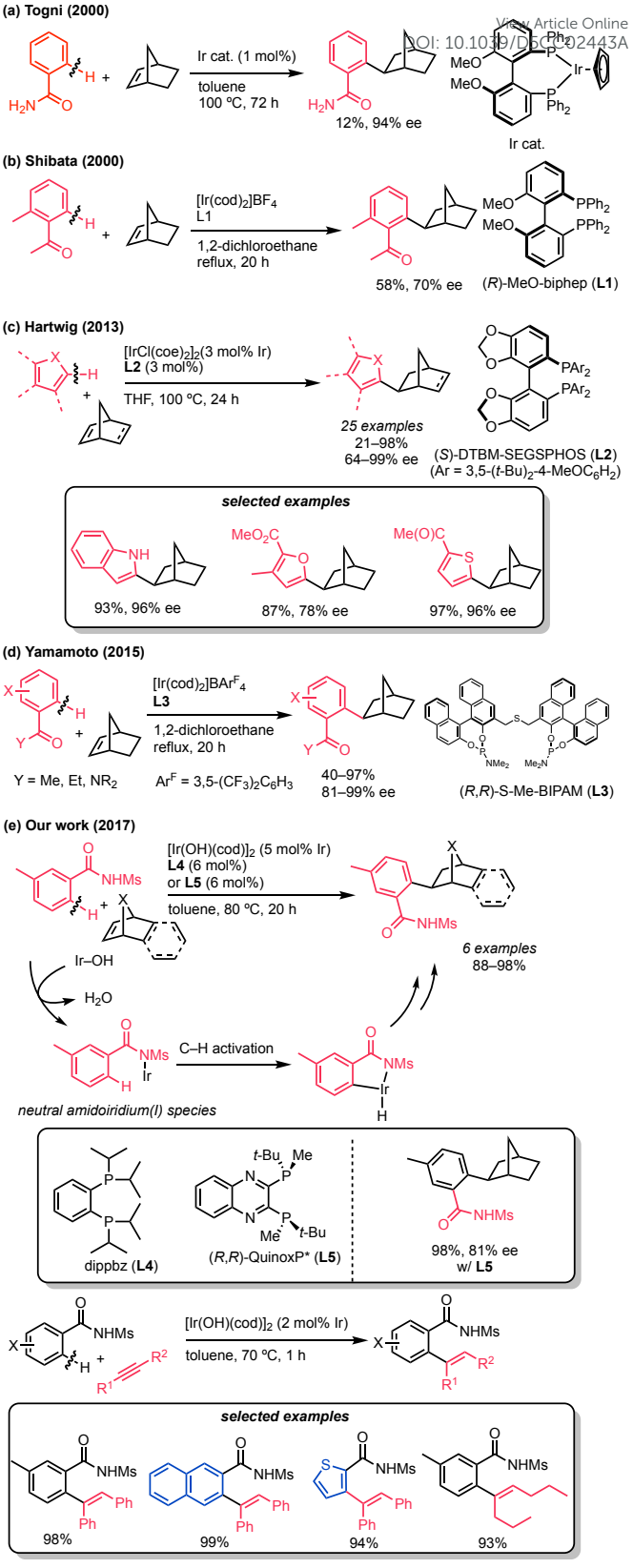
The first example of iridium-catalysed enantioselective aromatic C–H bond addition, so called hydroarylation, was reported more than two decades ago. In 2000, Togni and co-workers reported an iridium-catalysed *ortho*-C–H addition of benzamide to 2-norbornene (Scheme 2a).[12] They demonstrated that the Ir(I) catalyst, originally developed for the enantioselective hydroamination of 2-norbornene, is suitable for the asymmetric hydroarylation using benzamide. In this reaction, the CpIr(I) catalyst ligating (*R*)-MeO-biphep (**L1**) catalysed the enantioselective addition of the aromatic C–H bond to 2-norbornene to give the *exo*-adduct with 94% ee, albeit in low yield (12%). A similar catalytic system was used by Shibata and co-workers in the hydroarylation of 2-norbornene with 2'-methylacetophenone (Scheme 2b).[13] They used a cationic Ir(I) complex derived from $[Ir(cod)_2]BF_4$ and (*R*)-MeO-biphep (**L1**) to give the alkylated compound with 70% ee.

In 2013, Hartwig and co-workers demonstrated highly enantioselective hydroheteroarylation of bicycloalkenes, including 2-norbornene, with heteroaromatic compounds (Scheme 2c).[14] The regioselective C–H bond cleavage occurred at the C-2 position even when unprotected indoles were used. The neutral iridium complex bearing bulky (*S*)-DTBM-SEGPHOS (**L2**) converted a variety of heteroarenes, such as indoles, pyrroles, benzofurans, and benzothiophenes into alkylated compounds in low to high yields (21–98%) with high enantioselectivity (64–99% ee).

Yamamoto and co-workers demonstrated that the iridium complex bearing a tailor-made ligand, (*S*)-S-Me-BIPAM (**L3**), is suitable for the asymmetric hydroarylation of bicycloalkenes with aromatic ketones, benzamides, and aniline derivatives with high reactivity and enantioselectivity (Scheme 2d).[15]

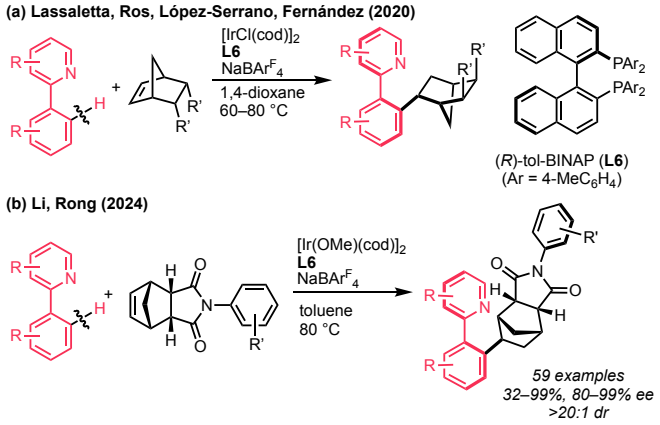
In 2017, our group reported the stereoselective hydroarylation of bicycloalkenes with *N*-sulfonylbenzamides (Scheme 2e).[16] In this reaction, the amidoiridium complex was generated as a key intermediate from *N*-sulfonylbenzamides and an Ir-OH complex bearing 1,2-bis(diisopropylphosphino)benzene (dippbz, **L4**) to catalyse the alkylation. The use of or (*R*,*R*)-QuinoxP* (**L5**) allowed the enantioselective alkylation with good enantioselectivity (98% yield, 81% ee). The same catalytic system was also effective for hydroarylation of alkynes.

In 2020, Lassaletta, Ros, López-Serrano, Fernández, and co-workers developed the atroposelective desymmetric alkylation of 2-pyridylarenes with bicycloalkenes (Scheme 3a).[17] A cationic iridium complex having (*R*)-tol-BINAP (**L6**) was shown to be an efficient catalytic system for achieving both high *exo*-selectivity and enantioselectivity (>20:1 *exo* selective and 89– >99% ee).



Scheme 2. Enantioselective hydroarylation of bicycloalkenes

Later, Li, Rong, and co-workers demonstrated the same cationic iridium/(*R*)-tol-BINAP system is suitable for accessing distal biaxial atropisomers (Scheme 3b).[18] Thus, the diastereo- and



Scheme 3. Diastereoselective hydroarylation of bicycloalkenes

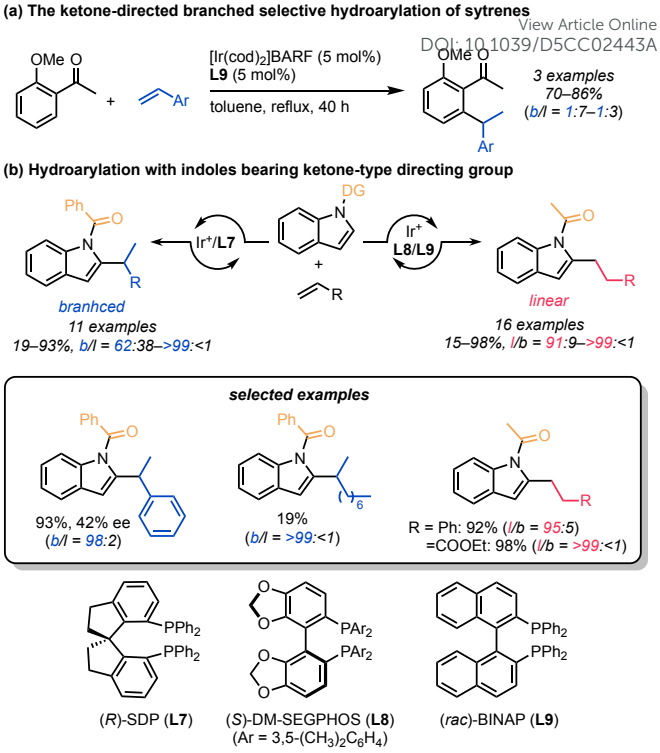
enantioselective hydroarylation of bicycloalkenes with 2-arylisoquinolines proceeded to give the remote biaxial chiral molecules in high selectivity (up to 99% ee).

Hydroarylation of styrenes and α-olefins

In the hydroarylation of terminal alkenes, the position of the addition of the aryl group determines whether a linear or branched product is formed. Controlling the regioselectivity of this addition has been the attractive subject, with efforts focused on the choice of aryl substrates, accepter alkenes, catalyst metals, and ligands.[19] In branched selective addition reactions, compounds with a stereogenic centre can be obtained, and attempts have been made to simultaneously control both the site of addition and the enantioselectivity. Such dual control has been successfully achieved in several reaction systems in recent years.

In 2008, Shibata and co-workers reported the first examples of iridium-catalysed hydroarylation of styrene, which is a minimally activated and unstrained alkene. The ketone-directed hydroarylation of styrenes took place in the presence of an iridium/BINAP (**L9**) catalyst (Scheme 4a).[13] Unfortunately, the alkylated products were obtained as a mixture of linear and branched products with low to moderate regioselectivities (3:1 to 7:1). Later, the same group developed the regiodivergent hydroarylation of styrenes with indoles, where the directing group on the nitrogen of the indoles controlled the regioselectivity (Scheme 4b).[20] The indole derivatives bearing the acetyl group reacted with styrenes, acrylonitrile, methyl vinyl ketone, and acrylates to give the corresponding linear products, with the aid of (*S*)-DM-SEGPHOS (**L8**) or (*rac*)-BINAP (**L9**). In contrast, their benzoyl analogues predominantly provided the branched products with (*R*)-SDP ligand (**L7**) using the styrenes as alkenes. This directing group-controlled regioselective hydroarylation is an attractive strategy, particularly for asymmetric reactions because it offers the possibility of using various commercially available chiral ligands. However, the enantioselectivity of the branched product reported in Shibata's work is moderate (42% ee).

In this context, our group has recently developed iridium-catalysed enantioselective and branched selective hydroarylation of terminal alkenes with indole derivatives



Scheme 4. Directing-group-controlled branched selective hydroarylation

under directing group control conditions (Scheme 5a).[21] We found that the benzimidazole-type directing groups preferentially gave the branched products, especially the *N*-methylbenzimidazolyl group, with high enantioselectivities even when using (*R*)-BINAP (**L9**) as a chiral ligand. Not only styrene derivatives but also α-olefins, such as allylsilanes, gave the branched alkylated products, maintaining both high regio- and enantioselectivity (up to b/l = >99:1 and up to 91% ee). Very recently, we have extended this directing group-controlled strategy to the branched selective and enantioselective hydroarylation of the 1,1-disubstituted alkenes (Scheme 5b).[22] Such enantioselective hydroarylation of 1,1-disubstituted alkenes, especially the branched selective reaction, has been reported mainly in an intramolecular fashion, and the intermolecular variants were still limited, probably due to steric hindrance. Based on the present strategy, we tested the regio- and enantioselective hydroarylation of 1,1-disubstituted alkenes with the aim of constructing all-carbon quaternary stereocentres. Surprisingly, indoles and pyrroles bearing *N*-methylbenzimidazole as a directing group were reacted with α-alkylstyrenes to give the desired products with quaternary stereocentres. Control experiments showed that the *N*-methylbenzimidazole is a privileged directing group, and other azole-type groups, such as benzoxazole and benzothiazole, gave no product. This transformation could provide a practical method for the construction of acyclic all-carbon quaternary centres with 100% atom economy. The *N*-methylbenzimidazole group attached to the indole nitrogen can be converted to a proton by treating the product with MeOMs followed by NaOMe.

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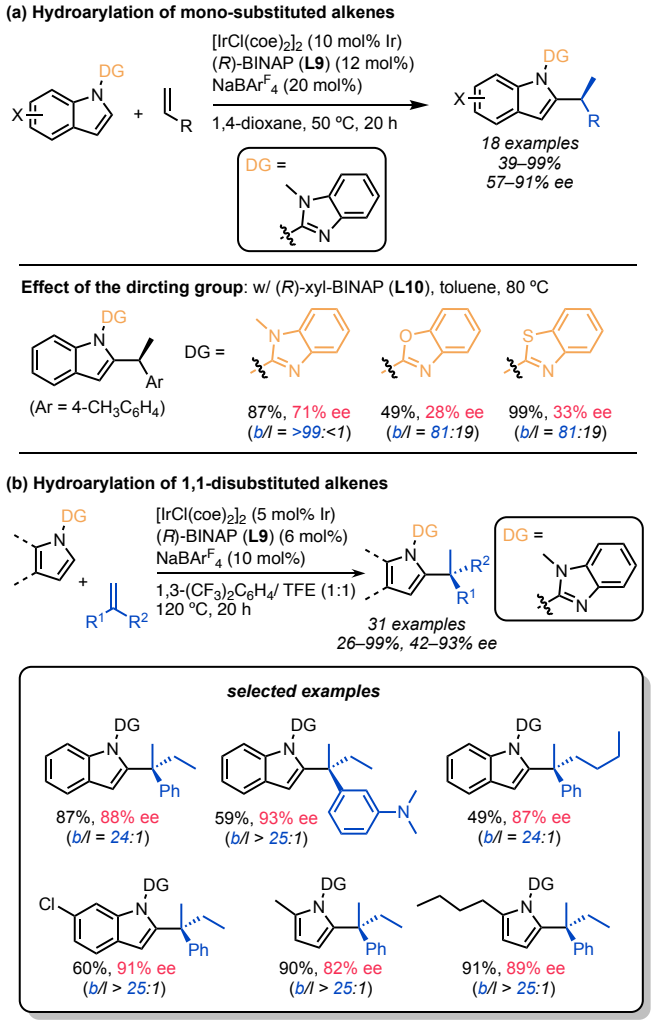
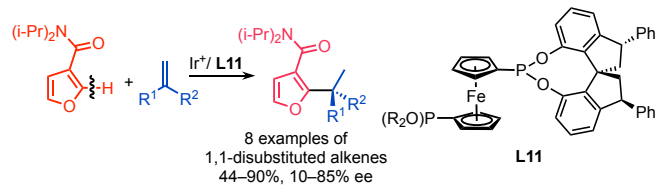


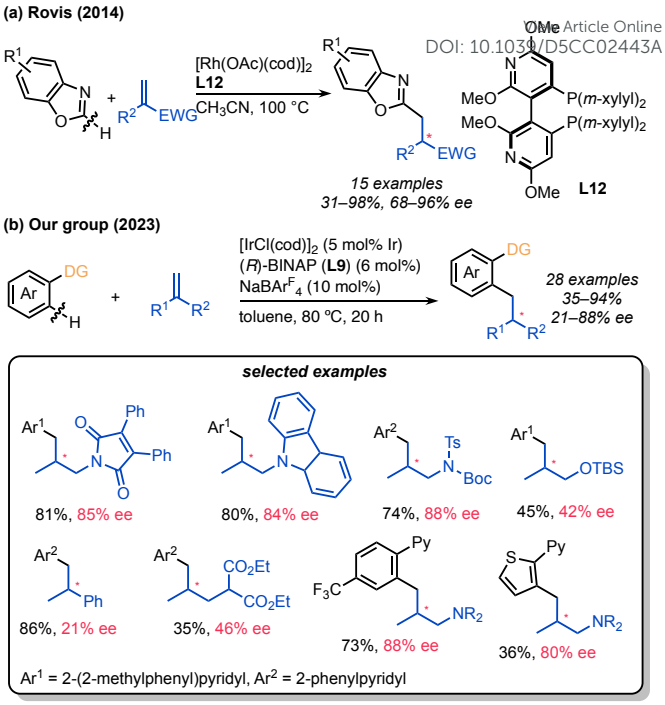
Scheme 5. Directing-group-controlled branched selective hydroarylation

A similar hydroarylation of 1,1-disubstituted alkenes was also recently reported by the Bower's group using a tailor-made ferrocene-based diphosphine ligand **L11** (Scheme 6).[23]

A related enantioselective hydroarylation of 1,1-disubstituted alkenes using linear selectivity has also been reported. Rovis and co-workers developed the linear and enantioselective hydroheteroarylation of α-alkyl acrylates with benzoxazoles under rhodium catalysis (Scheme 7a).[24] In 2022, our group reported the linear and enantioselective hydroarylation of 1,1-disubstituted alkenes with 2-arylpyridines under cationic iridium-catalysed conditions (Scheme 7b).[25] Methallylamine derivatives, bearing the phthalimide,



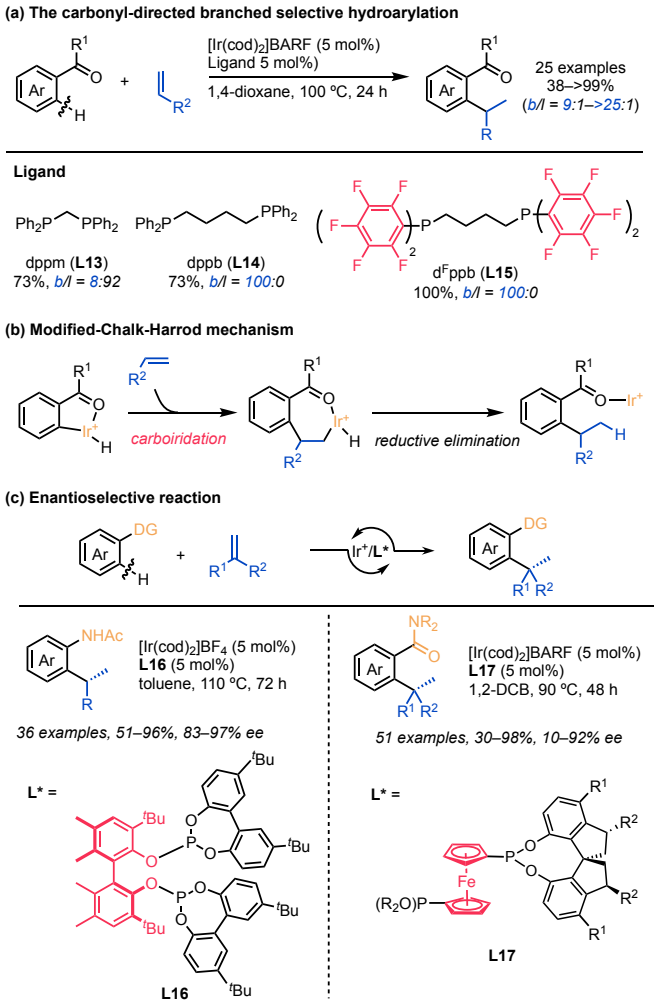
Scheme 6. Ligand-controlled branched selective hydroarylation of 1,1-disubstituted alkenes



Scheme 7. Linear- and enantioselective hydroarylation of 1,1-disubstituted alkenes

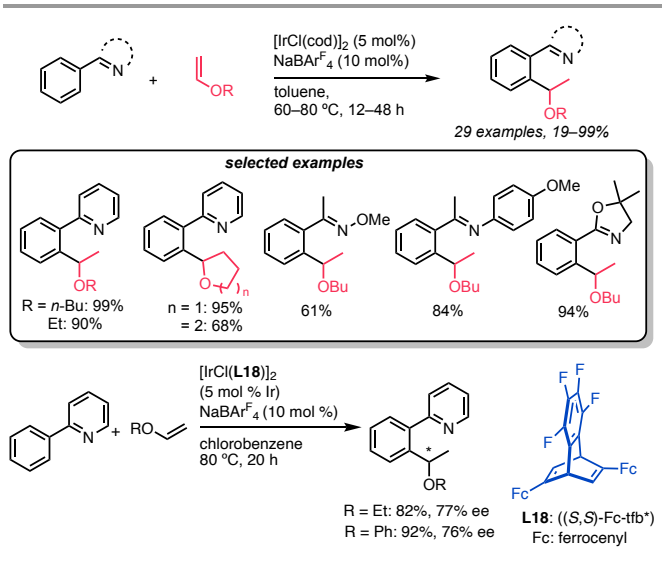
maleimide, carbazole, and acyclic substituents, showed high enantioselectivity towards the β-chiral amines (up to 88% ee). On the other hand, 1,1-disubstituted alkenes with other functional groups, such as methallyl alcohol, α-methylstyrenes, and diester moieties, were less effective in terms of stereoselective reactions.

The ligand-controlled regio- and enantioselective hydroarylation reaction can provide another approach to achieve high selectivity by fine-tuning the chiral environment. In 2014, Bower and co-workers developed the cationic iridium-catalysed branched selective hydroarylation of styrenes and α-olefins enabled by ligand tuning (Scheme 8a).[26] Under the conditions provided by the iridium/diphosphine complex, they found that the regioselectivity reversed from b/l = 8:92 to 100:0 as the bite angle of the diphosphine ligand was increased. In addition, the chemical efficiency was improved from 28% yield to quantitative yield by using d^Fppb (**L15**), which is the pentafluorophenyl analogue of dppb (**L14**). The DFT calculation study carried out by Huang and Liu indicated that the reaction proceeded by a modified Chalk-Harrod type mechanism, and the regioselectivity was determined by the steric factors between substrates and aryl groups on the ligand when using wide bite angles, such as d^Fppb (**L15**) and dppb (**L14**) (Scheme 8b).[27] This catalytic system was applicable to the branched selective alkylation of aromatic amides, ketones, esters, and anilides, even using α-olefins, such as propene.[28] Later, the same group successfully developed the iridium-catalysed branched selective and enantioselective hydroarylation of alkenes using anilide-directed systems (Scheme 8c).[29] The high regio- and enantioselective reactions were achieved by using BiPhePhos-like chiral diphosphine ligand **L16** to give the tertiary benzylic stereocentres (up to b/l >25:1, up to 97% ee). They also

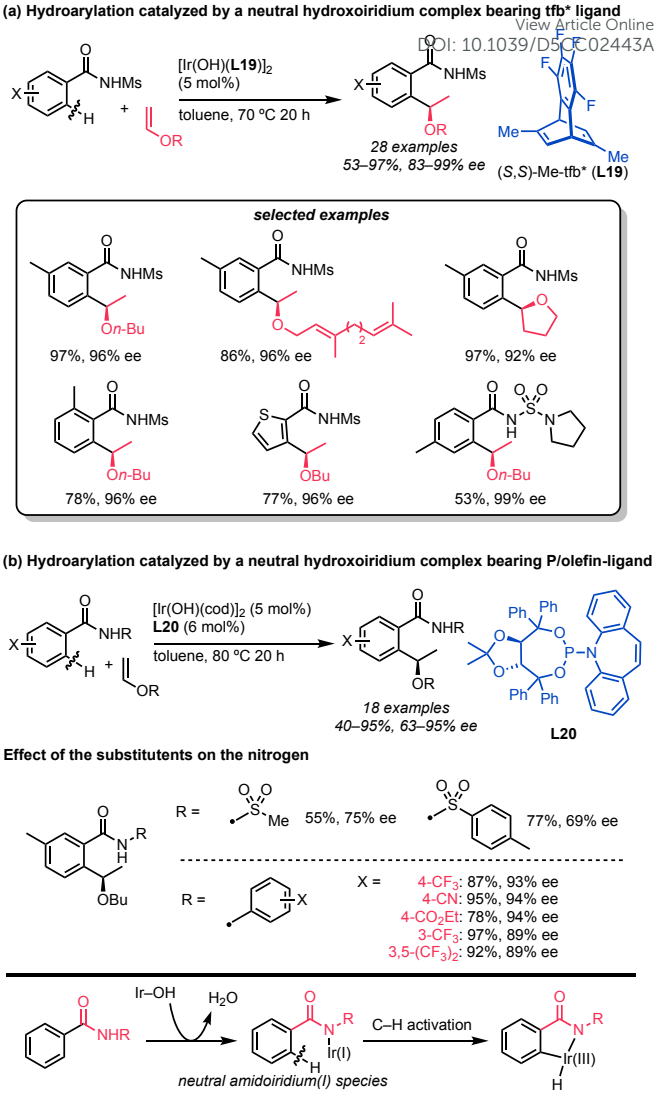


Scheme 8. Ligand-controlled branched selective hydroarylation reactions

developed benzamide-directed regio- and enantioselective hydroarylation utilizing newly designed SPINOL-type diphosphine ligands **L17**.[23]



Scheme 9. Branched selective hydroarylation of vinyl ethers

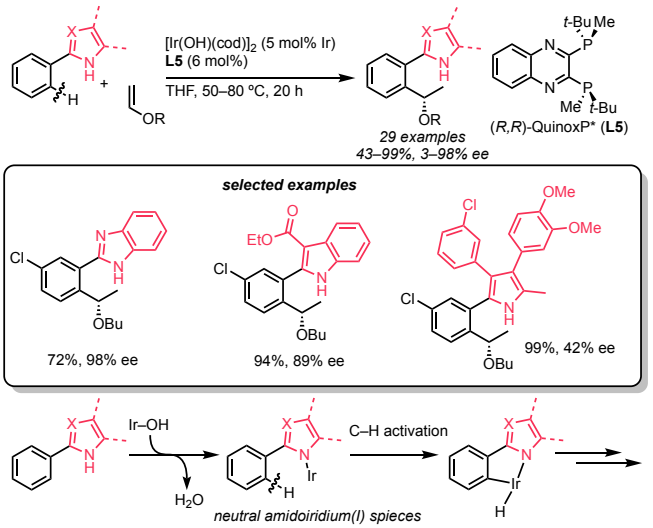


Scheme 10. Branched and enantioselective hydroarylation of vinyl ethers

Hydroarylation of vinyl ethers

We have developed a series of iridium-catalysed enantioselective hydroarylation using vinyl or alkenyl ethers as acceptors. As an initial reaction that led us to study asymmetric hydroarylation reactions, in 2015, we reported the branched selective hydroarylation of vinyl ethers *via* aryl C–H bond activation using imine-based directing groups. A cationic iridium complex coordinated with a cod ligand (1,5-cyclooctadiene) cleaved the ortho C–H bond and unconventional branched selective alkylation proceeded to give the benzylic ethers (Scheme 9).[30] Since 1,5-cyclooctadiene acts as a chelating ligand of the Ir complex, the use of chiral diene ligands as a chiral ligand for the asymmetric hydroarylation was employed. The Ir complex coordinated with a chiral diene ligand based on a tetrafluorobenzobarrelene scaffold (**L18**) showed a high catalytic activity and good enantioselectivity in the hydroarylation reaction.

We have also successfully developed highly enantioselective hydroarylation of vinyl ethers using convertible directing group *N*-sulfonylbenzamides (Scheme 10a).[31] The

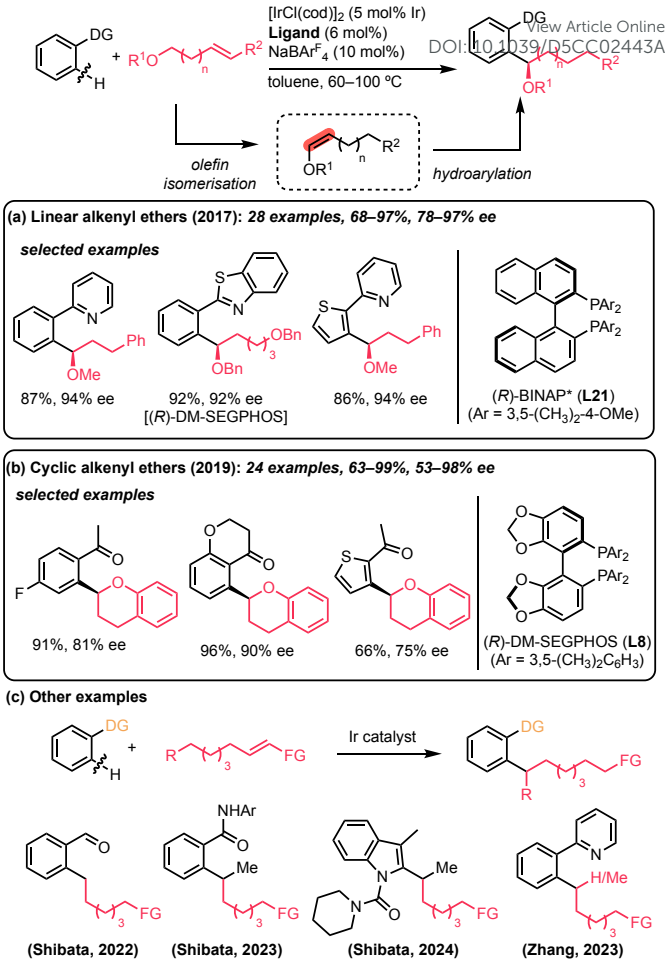


Scheme 11. Branched and enantioselective hydroarylation with azole-containing arenes

hydroxoiridium/chiral diene complex ([Ir(OH)(**L19**)]$_2$) efficiently catalysed branched selective and enantioselective C–H bond addition to give ortho-alkylated *N*-mesylbenzamide in good yields (23–97%) with high enantioselectivity (82–99% ee). Compared to the imine-based directing groups, the *N*-sulfonyl group is readily converted into various functional groups, such as ester, alcohol, aldehyde, amide, and lactone. In this series, we found that the hydroarylation of vinyl ethers with *N*-sulfonylbenzamides is also catalysed by an iridium/chiral phosphoramidate-olefin (**L20**) complex (Scheme 10b).[32] Benzamides bearing an electron-deficient aryl group on the nitrogen displayed a high reactivity as well as high enantioselectivity (up to 95% ee).

As shown in Scheme 11, we further extended this hydroxoiridium-catalysed branched selective and enantioselective hydroarylation of vinyl ethers with azole-containing arenes.[33] Thus, a variety of azole-type directing groups, including 2-arylbenzimidazoles, pyrroles, and indoles, were compatible, yielding chiral benzylic ethers at 50 °C with moderate to high enantioselectivities (up to 98% ee). The present reaction required the P-chiral ligand, QuinoxP* (**L5**), for high reactivity and enantioselectivity.

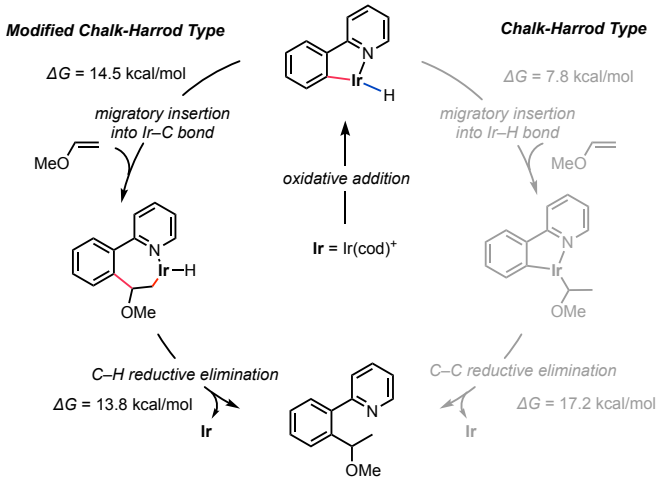
The combined reaction methodology of alkene isomerisation and hydroarylation is an attractive transformation that introduces an aryl group at the desired position using readily available alkenes.[34] We constructed the enantioselective hydroarylation of alkenyl ethers *via* olefin isomerisation (Scheme 12).[35] The cationic iridium complex coordinated with a chiral diphosphine ligand **L21** promoted both the olefin isomerisation and the subsequent hydroarylation reaction. Thus, in the reaction of linear alkenyl ethers, the corresponding chiral benzylic ethers were obtained in high yields with high enantioselectivity (Scheme 12a).[35a] The same strategy can also be successfully applied to the enantioselective synthesis of flavan derivatives (Scheme 12b), where aromatic ketones were introduced into the flavan skeleton.[35b] Following our research findings, several similar



Scheme 12. Chain-walking type enantioselective hydroarylation of alkenyl ethers

reports on iridium-catalysed sequential olefin isomerisation and hydroarylations were subsequently developed by Shibata and Zhang (Scheme 12c).[36]

Huang and Zhang provided deeper insights into the mechanism of our catalytic reaction through DFT calculations.[37] They showed that the branched selective hydroarylation catalysed by the iridium complex proceeds by an



Scheme 13. DFT calculations by Huang and Zhang

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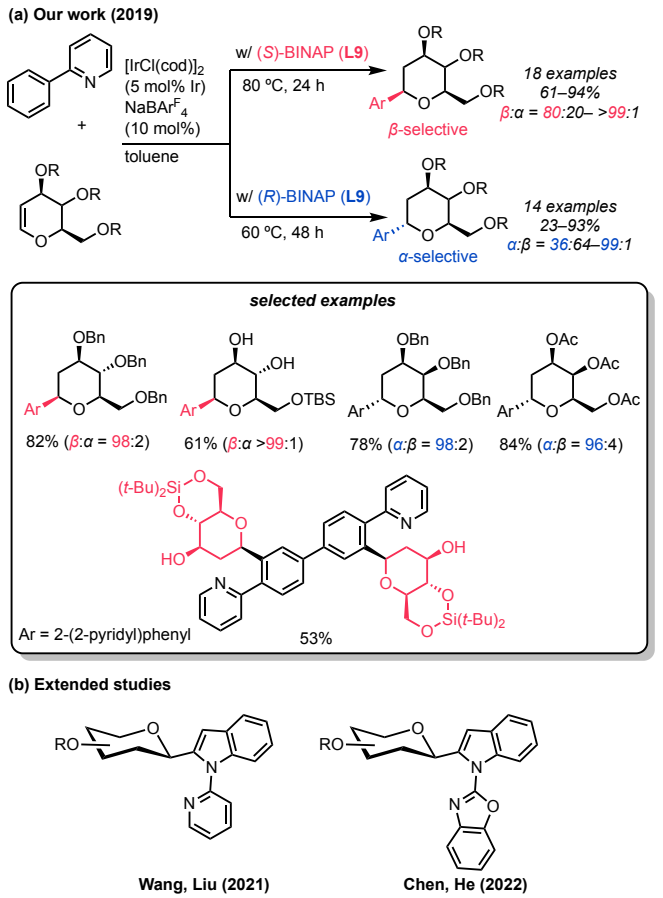
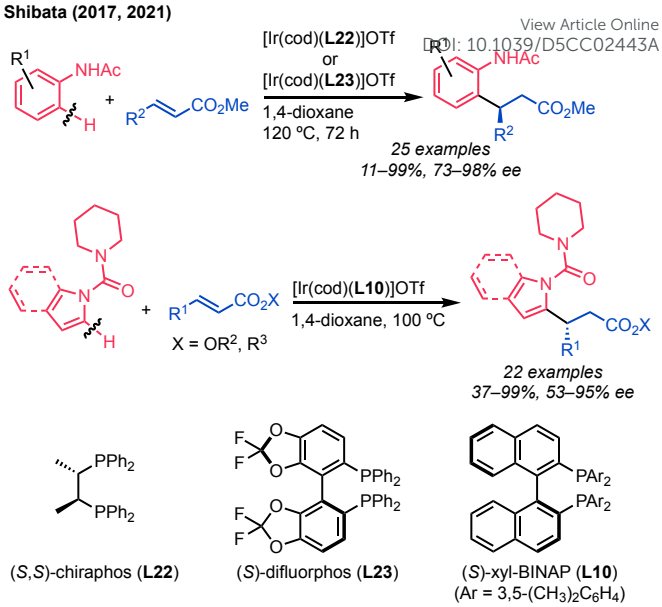
unconventional modified Chalk-Harrod type mechanism, involving the insertion into the Ir–C bond followed by C–H reductive elimination (Scheme 13).

2-Deoxy-*C*-glycosides are attractive synthetic targets due to their high stability and resistance to enzymatic hydrolysis process, induced by their C–C glycosidic linkage.[38] In particular, 2-deoxy-*C*-aryl glycosides have been used in drug development, including SGLT2 inhibitors such as dapagliflozin.[39] Therefore, the development of efficient synthetic methods for *C*-aryl glycosides has attracted much interest. Building on the regioselective aryl C–H addition to alkenyl ethers achieved with the iridium catalysis, we have successfully synthesised α- and β-C-glycosyl arenes using glycals as the cyclic vinyl ether moiety representing sugar derivatives (Scheme 14a).[40] The diastereoselective hydroarylation of glycals was achieved by changing the absolute configuration of the chiral diphosphine ligands. Thus, in the presence of a cationic iridium catalyst, the ortho-C–H bond of 2-phenylpyridine was regioselectively added to glycals using the (*R*)- or (*S*)-BINAP (**L9**) at an optimised temperature, leading to α- or β-2-deoxy-C-aryl glycosides, respectively, with high diastereoselectivity. Following our work on the regiodivergent hydroarylation of glycals with 2-arylpyridines, the groups of Liu and Wang, and of Chen and He independently showed that the indole C–H bond is also β-selectively added to the glycals in the presence of the iridium/BINAP catalyst (Scheme 14b).[41]



Scheme 14. Ligand-controlled stereoselective hydroarylation of glycals



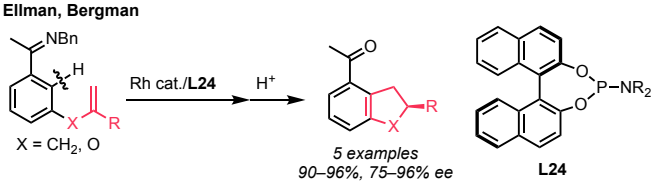
Scheme 15. Enantioselective hydroarylation of enones

Hydroarylation of enones

The hydroarylation of the synthetically valuable alkenes, such as α,β-unsaturated carbonyl compounds, provides a new approach that achieves atom- and step-efficient synthesis. The Shibata group has developed the iridium-catalysed hydroarylation of electron-deficient alkenes, such as α,β-unsaturated carbonyl compounds (Scheme 15).[42] For the enantioselective variants, Shibata and co-workers reported in 2017 the iridium-catalysed formal C–H conjugated addition to β-substituted acrylates with acetanilide.[42c] The aryl group was selectively added to the β-position of the acrylates, providing the chiral δ-amino acid derivatives. This iridium-catalysed regio- and enantioselective addition to acrylates has also been applied to the benzamide-directed system or to hydroarylation using pyrroles in an enantioselective manner.[42e]

2-2. Intramolecular addition of C(sp²)–H bonds to alkenes

Intramolecular asymmetric hydroarylation catalysed by transition-metal complexes has been recognised as a powerful tool to the synthesis of enantioenriched cyclic compounds with perfect atom economy. The pioneering studies were carried out by Ellman and Bergman, who reported the asymmetric cyclisation *via* C–H activation in the presence of the Rh/phosphoramidite **L24** complex (Scheme 16).[43] 5-*Endo*-



Scheme 16. Rh-catalysed enantioselective intramolecular hydroarylation

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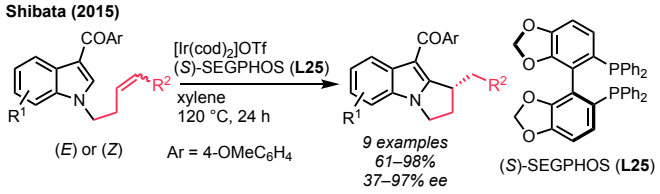
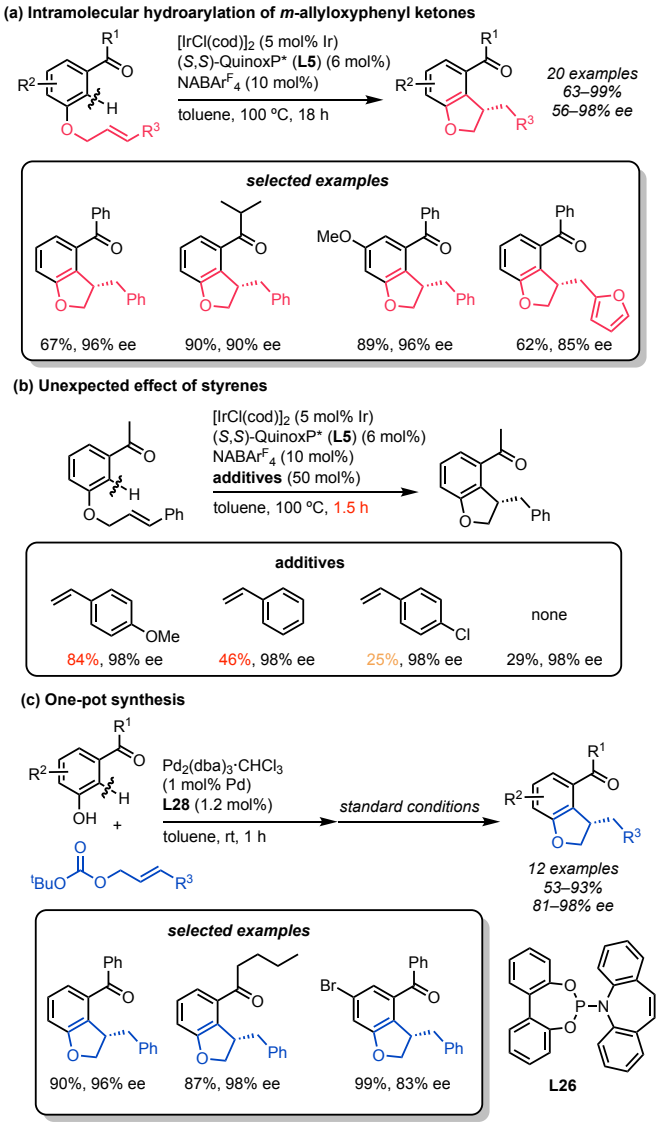


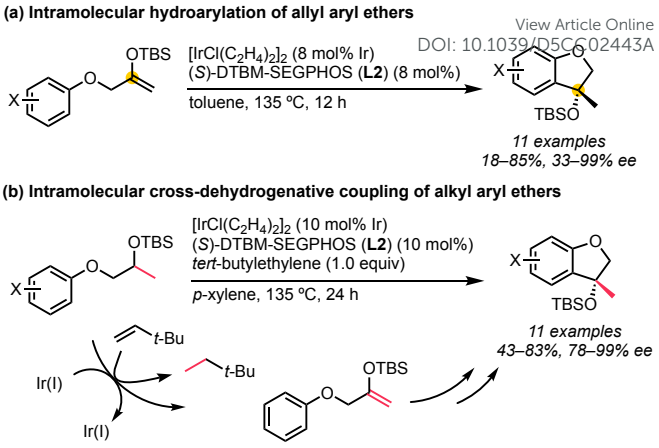
Scheme 17. Ir-catalysed enantioselective intramolecular hydroarylation

cyclisation led to the chiral indane, indolines, and dihydrobenzofuran with moderate to high enantioselectivity (70–96% ee).

The iridium catalysis for enantioselective intramolecular hydroarylation was developed by Shibata and co-workers, who reported the 5-*exo*-cyclisation reaction of *N*-alkenylindoles in 2015, and the cyclisation of benzene-tethered fumarate in 2018. Both reactions used the carbonyl oxygen as a directing group for C–H activation, achieving high enantioselectivity (Scheme 17).[42d, 44]



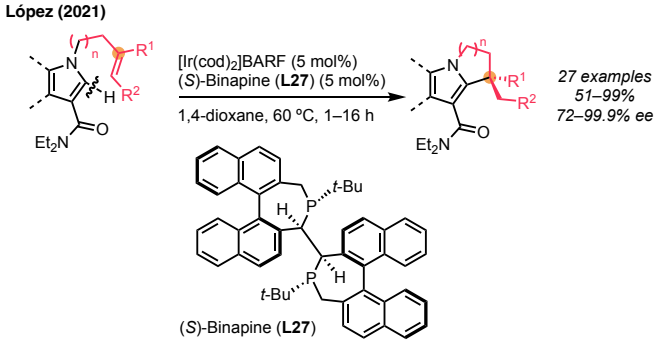
Scheme 18. Enantioselective intramolecular hydroarylation of *m*-allyloxyphenyl ketones



Scheme 19. Enantioselective intramolecular hydroarylation of alkyl- and alkenyl ethers

Around the same time as Cavallo and Rueping,[45] we reported highly enantioselective intramolecular hydroarylation of *m*-allyloxyphenyl ketones catalysed by a cationic iridium/(*S*,*S*)-QuinoxP* (**L5**) or (*S*)-difluorphos (**L23**) complex (Scheme 18).[46] The cyclisation of a variety of *m*-cinnamyloxyphenyl ketones led to the 3-substituted dihydrobenzofurans in high yields and high enantioselectivities (up to >99% yield and 98% ee). Furthermore, it was unexpectedly found that the presence of *p*-methoxystyrene drastically increased the reaction efficiency compared to the standard condition (Scheme 18b). Thus, the cyclisation product was obtained in a high yield of 84% compared to 29% under the standard conditions, despite the shorter reaction time of 1.5 h. Notably, *p*-methoxystyrene did not participate in the reaction. Conversely, more electron-deficient styrene, such as *p*-chlorostyrene, or styrene showed no acceleration of the reaction (25% and 46% yields, respectively, for 1 h). Since the *m*-cinnamyloxyphenyl ketones can be prepared under Pd-catalysed allylic substitution conditions, we next focused on the synthesis of 3-substituted dihydrobenzofurans by a combination of intermolecular Pd-catalysed allylic substitution and Ir-catalysed intramolecular hydroarylation (Scheme 18c). Unfortunately, however, the desired two sequential reactions did not occur under coexisting Pd and Ir catalytic systems. Instead, a one-pot strategy with no work-up or purification in the first Pd-catalysed reaction worked well. Thus, the treatment of *m*-hydroxyacetophenone with *tert*-butyl cinnamyl carbonate in the presence of a Pd/P-olefin ligand **L26** complex in toluene for 1 h, followed by an Ir^{+}/(*S*,*S*)-QuinoxP* (**L5**) complex at 100 °C for 18 h, gave the dihydrobenzofuran in high yields with high enantioselectivity (52–99%, 81–98% ee).

Suginome and Ohmura developed an iridium system for the synthesis of enantio-enriched dihydrobenzofuran, realising directing group-free conditions (Scheme 19).[47] They reported that a neutral iridium complex ligating bulky (*S*)-DTBM-SEGPHOS (**L2**) catalysed the cyclisation of allylic aryl ethers. They found that the substituent on the double bond hindered the olefin isomerisation and the corresponding dihydrobenzofuran was obtained in moderate to high yields (up to 85%) and high enantioselectivities (Scheme 19a, up to 99%



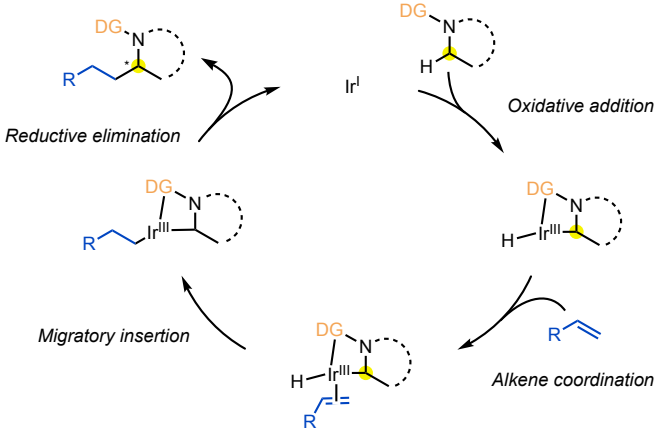
Scheme 20. Intramolecular enantioselective hydroarylation with heteroaromatic compounds

ee).[47a] The same group also reported the cross-dehydrogenative coupling strategy, in which a C–C bond is formed from two C–H bonds, to alkyl aryl ethers (Scheme 19b).[47b]

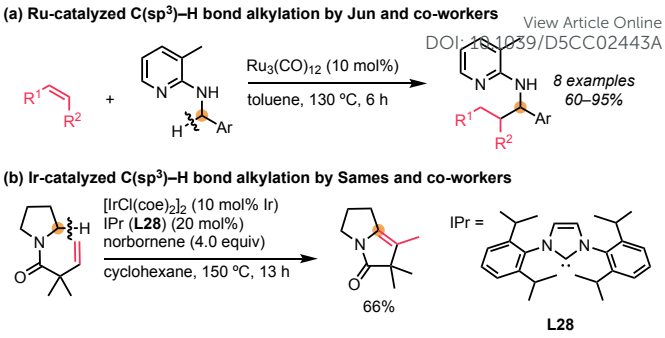
In 2021, López and co-workers reported intramolecular hydroarylation with heteroaromatic compounds, achieving 5-, 6-, and 7-exo-cyclisation of *N*-alkenyl pyrroles and indoles bearing 1,1-disubstituted tethers (Scheme 20).[48] In this reaction, a cationic iridium/(S)-Binapine (**L27**) complex efficiently catalysed the reaction to give the cyclic compounds with high enantioselectivity up to >99.5 % ee. In addition, the same group has recently developed the intramolecular hydroarylation of allene-tethered pyrroles and indoles.[49]

3. Iridium-Catalysed Addition of C(sp³)–H Bond

As previously mentioned, transition-metal-catalysed direct C–H functionalisation is a highly efficient approach for achieving step- and atom-economical transformations. Nevertheless, the activation of C(sp³)–H bonds remains challenging due to their intrinsic inertness, high bond-dissociation energies, and prevalence in organic molecules.[50] Directing-group-assisted C(sp3)–H bond alkylation with alkenes and alkynes has attracted considerable attention in recent decades. The C(sp³)–H bond adjacent to nitrogen is relatively reactive towards transition metals, enabling the formation of new C–C bonds. The direct alkylation method is one of the most efficient ways



Scheme 21. General catalytic cycle of Ir-catalysed C(sp³)–H alkylation adjacent to nitrogen



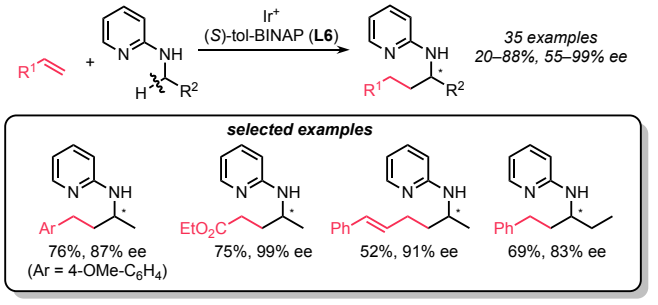
Scheme 22. Pioneering works of C(cp³)–H addition to alkenes

of producing a variety of chiral amines, which are fundamental structural motifs in natural products and biologically active compounds.[51] Iridium catalysts have also been used for the stereoselective C–C bond formation via C(sp³)–H bond activation. This is achieved by designing suitable directing groups and selecting appropriate chiral ligands. The general catalytic cycle for iridium-catalysed C(sp³)–H alkylation adjacent to nitrogen is shown in Scheme 21. As illustrated, the chelation-assisted oxidative addition of the C(sp³)–H bond forms a metallacycle, with the directing group playing a pivotal role.[52]

3-1. Addition of C(sp³)–H bonds adjacent to heteroatoms to alkenes

In 1998, Jun and co-workers reported pioneering work on the catalytic direct alkylation of C(sp³)–H bonds adjacent to the nitrogen atom using Ru catalysts (Scheme 22a).[53] The alkylation of benzylamines having the 3-methyl-pyridyl group as the directing group proceeded with terminal and internal alkenes to give the corresponding adduct in high yields. The first application of iridium catalysts to C(sp³)–H bond addition reaction was reported by Sames and co-workers, where the Ir/IPr (**L28**) complex catalysed the intramolecular 5-*exo* cyclisation (Scheme 22b).[54]

Shibata and co-workers reported the iridium-catalysed enantioselective alkylation of 2-(alkylamino)pyridines (Scheme 23).[55a] Similar to Jun's report, the pyridine-directed alkylation was carried out by the cationic iridium/(*S*)-tol-BINAP (**L6**) complex, which cleaved the C–H bond adjacent to a nitrogen atom to give the α-chiral amines with high enantioselectivity (up to 90% ee). Later, the same group extended the substrate scope to a variety of alkenes.[55b] Thus, in the presence of the cationic iridium catalyst, the C(sp³)–H bond enantioselectively added to the styrenes, α-olefins, dienes, acrylates, vinylsilanes, and



Scheme 23. Enantioselective alkylation of 2-(alkylamino)pyridines

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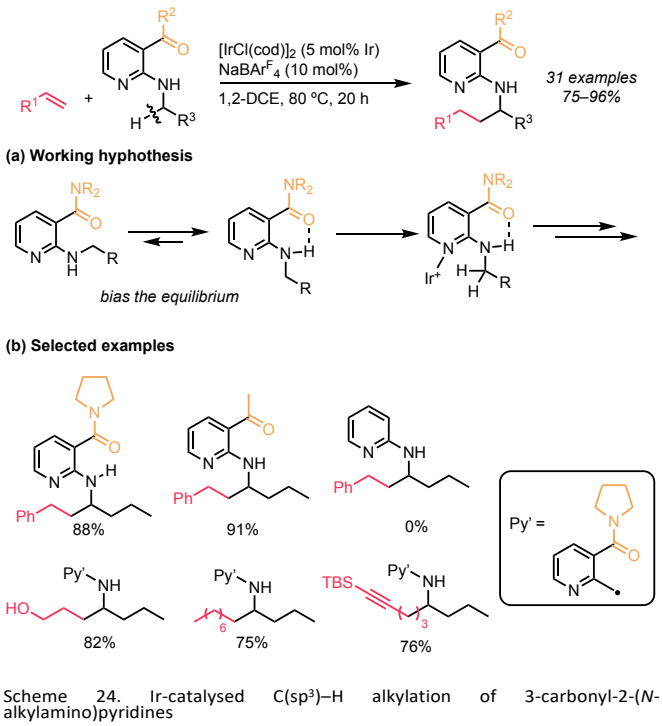
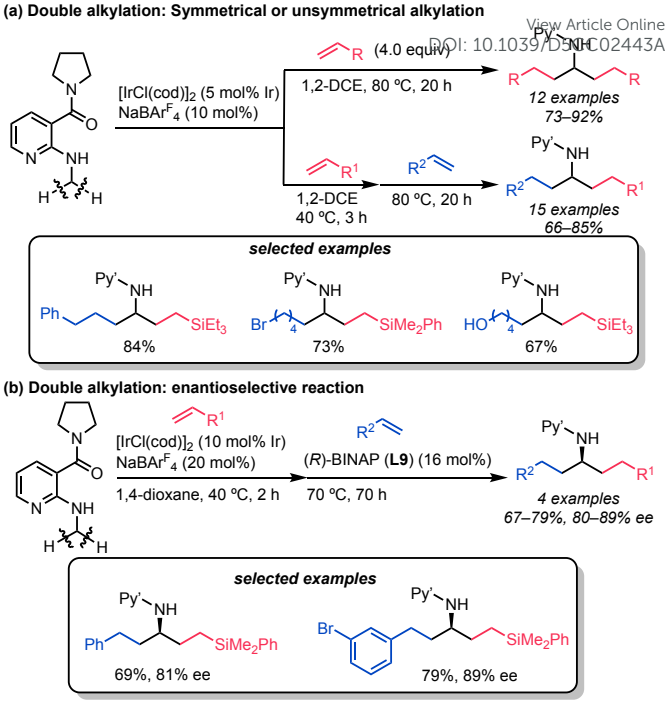


Scheme 24. Ir-catalysed C(sp³)–H alkylation of 3-carbonyl-2-(*N*-alkylamino)pyridines

allylsilanes to give the α-chiral amines with moderate to high enantioselectivities (55–99% ee).

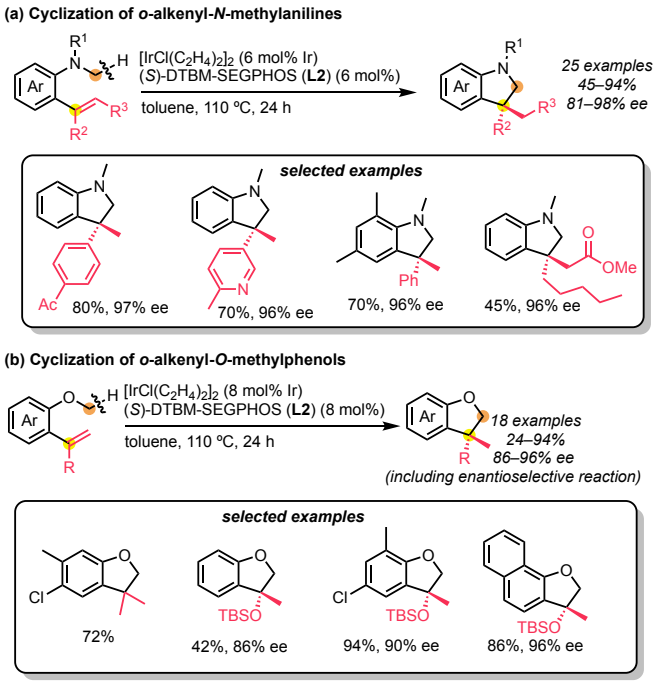
Our group has developed a series of C(sp³)–H alkylations of 2-(*N*-alkyl)aminopyridines substituted with an electron-withdrawing group at the 3-position.[56–62] Our initial strategy was to introduce a functional group on the pyridyl group capable of intramolecular hydrogen bonding with an N-H proton. We selected the amide group at the 3-position of the pyridyl group to tilt the equilibrium towards the reactive conformation by forming the hydrogen bond between the proton of the *N*-alkylamino group and the amide group (Scheme 24a).[56] In practice, in the presence of a cationic iridium catalyst having cyclooctadiene, the reaction of 2-(*N*-butylamino)pyridine with an amide group at the 3-position with styrene smoothly proceeded to give the alkylated compounds in high yield. In sharp contrast, the reaction of the unsubstituted 2-(*N*-butylamino)pyridine barely proceeded, supporting our hypothesis (Scheme 24b). A variety of alkenes, including styrenes, α-olefins, enynes, and acrylates, were well tolerated, thus giving the corresponding alkylation products in high yields (up to 89%). In addition to above results, the reaction system could also be applied to the double alkylation of a methylamine derivative by using an excess amount of alkenes (Scheme 25a).[57] Thus, the reaction of 2-(*N*-methylamino)pyridine bearing the amide group at the 3-position proceeded with styrenes, α-olefins, and vinylsilanes proceeded to give the corresponding alkylated products in uniformly high yields (ca. 86% yield). We have extended this double alkylation strategy to the asymmetric reaction using two different alkenes. The iridium-catalysed alkylation with vinylsilanes or 3,3,4,4,5,5,5-heptafluoropent-1-ene gave the mono-alkylated products, and the subsequent second alkylation with styrenes or α-olefins gave unsymmetrical amines in moderate to high yields (66–85%



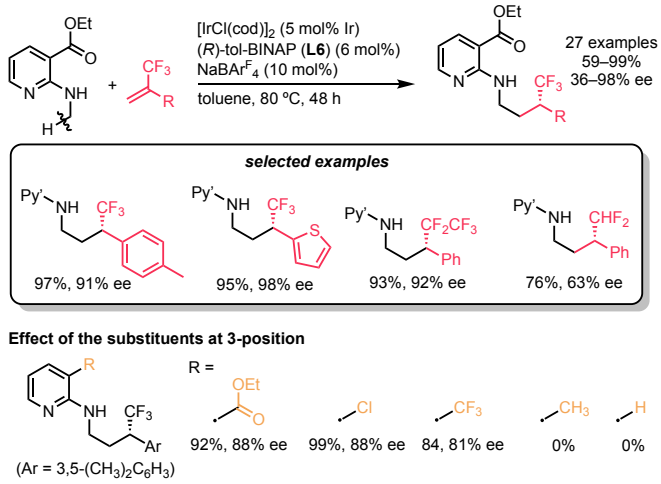
Scheme 25. Double alkylation of 2-(*N*-methylamino)pyridines having amide group at 3-position

yields) in a one-pot reaction. The asymmetric reaction was achieved by the addition of (*R*)-BINAP (**L9**) as a chiral ligand to give the α-chiral amines with high enantioselectivity (up to 89% ee, Scheme 25b). The pyridyl directing group was readily removed by treatment with MeOTf and NaOMe and converted to Boc-protected amines.

The successful examples of C(sp³)–H bond addition to the multi-substituted alkenes in an enantioselective manner are



Scheme 26. Intramolecular C(sp³)–H addition to multisubstituted alkene

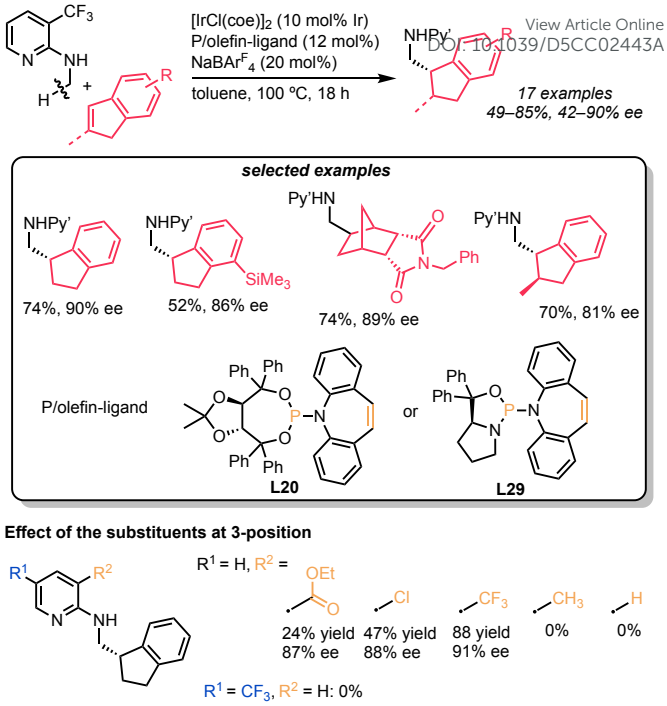


Scheme 27. Ir-catalysed enantioselective C(sp³)–H bond addition to α-CF_3 styrenes

limited and still challenging. As a representative example of such molecular transformations, Suginome and Ohmura reported the iridium-catalysed enantioselective intramolecular addition of C(sp³)–H bond across 1,1-disubstituted alkenes (Scheme 26).[58] The cyclisations of *ortho*-alkenyl-*N*-methylanilines or *ortho*-alkenyl-*O*-methylphenols were catalysed by a neutral iridium/diphosphine complex to give the indolines or dihydrobenzofurans with high enantioselectivities. These reactions were specifically and effectively catalysed by the use of the bulky diphosphine ligand, such as DTBM-SEGPHOS (**L2**). Based on the mechanistic experiments, it was clarified that 1) C–H cleavage is likely to be the rate-determining step and 2) the cyclic products are obtained by carboiridation and C–H reductive elimination. The authors also extended the intramolecular C(sp³)–H bond addition strategy to the *in situ* dehydrogenation/cyclisation process.[59]

In this line, we next focused on the enantioselective C(sp³)–H alkylation of 2-(*N*-methylamino)pyridines with multisubstituted alkenes. In 2021, we reported the asymmetric addition of the *N*-methyl C–H bond to α-(trifluoromethyl)styrenes using 3-ethoxycarbonylpyridine served as the directing group (Scheme 27).[60] The corresponding CF_3-containing chiral amines were obtained in high enantioselectivities (up to 98% ee) by a smooth C–H bond addition. The reaction efficiency was drastically influenced by the nature of the substituents at the 3-position of the pyridyl directing group. When the ethoxycarbonyl group was replaced by other electron-withdrawing groups, such as Cl and CF_3, the desired reaction proceeded smoothly. However, pyridines bearing Me, OMe, and F at the 3-position and Cl at the 5-position were unreactive. These results clearly indicated that both bulkiness and electron deficiency of the substituents were essential for the reaction efficiency.

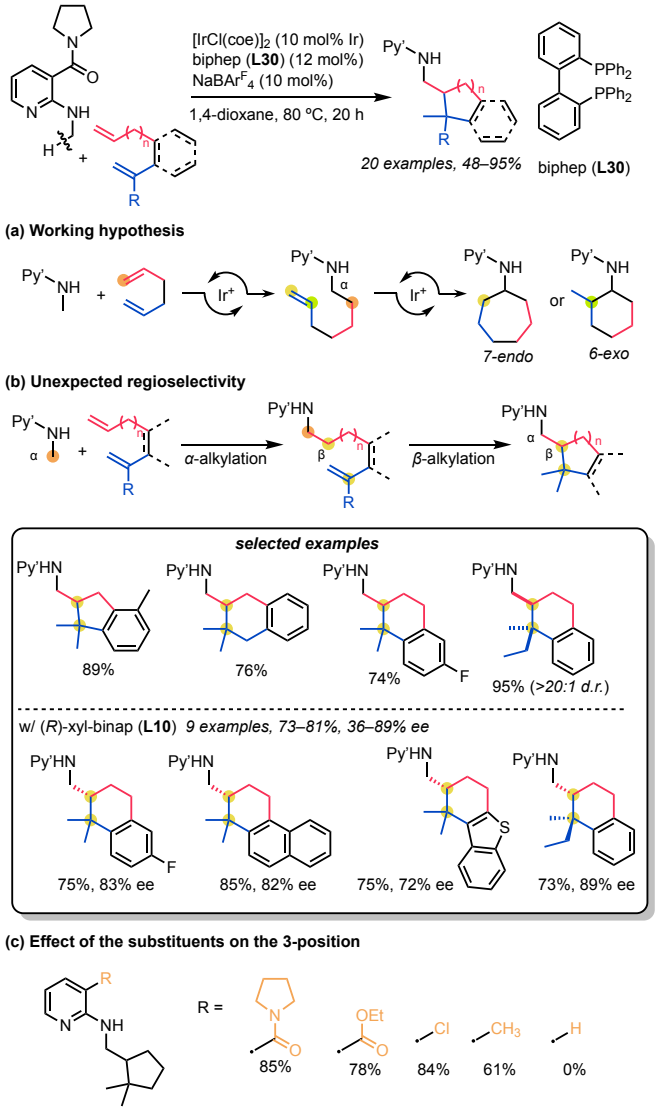
Similar patterns in the substituents of the directing group were found in the asymmetric C–H bond addition to internal alkenes. In 2022, we reported the iridium-catalysed C(sp³)–H alkylation with cyclic alkenes, such as indenes and norbornene derivatives (Scheme 28).[61] In contrast to the C–H alkylation of *N*-alkylaminopyridines reported by Shibata and our group, this



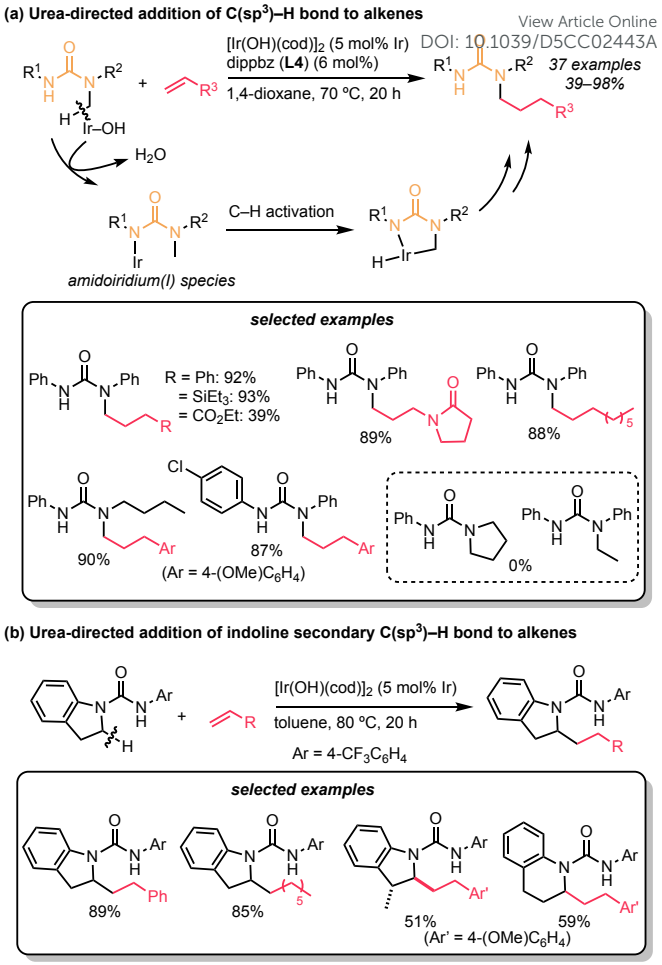
Scheme 28. Ir-catalysed enantioselective C(sp³)–H addition to internal alkenes

reaction was effectively catalysed by cationic iridium/phosphine-olefin catalysts. Thus, in the presence of $[IrCl(coe)_2]_2$ and $NaBAr^F_4$, the phosphoramidite-type P-olefin ligands (**L20**, **L29**) acted as ligands (3–88%, 17–91% ee), whereas diphosphine ligands, such as (*R*)-BINAP (**L9**) and (S)-SEGPHOS (**L25**), did not (0%). The substrate scope is relatively broad, and enantioselective C–H bond addition proceeded with moderate to high selectivity (42–91% ee), even when using trisubstituted alkenes (70%, 81% ee). The effect of the substituents at the 3-position on the pyridyl group was investigated, indicating that both bulkiness and electron-withdrawing properties promoted the reaction.

As the next target for iridium-catalysed C–H addition, we chose the reaction with α,ω-dienes (Scheme 29).[62] Based on the previously reported double alkylation of the *N*-methyl group bearing an amide moiety at the 3-position of the pyridyl directing group, we initially hypothesised that the reaction with 1,5-diene would yield the six- or seven-membered carbocycles, depending on whether *exo*- or *endo*-cyclisation occurred, the second alkylation could occur at the α-position of N-alkylamines (Scheme 29a). Interestingly, the 5-*exo*-cyclisation proceeded at the β-position, and the corresponding 5-membered carbocycles were obtained (Scheme 29b). This unexpected reaction proceeded even when benzene-linked and silicon- and nitrogen-tethered 1,5- or 1,6-dienes were used to provide the cyclic compounds in moderate to high yields (48–95% yields). The asymmetric reaction was also achieved by using the (*R*)-xyl-BINAP (**L10**) as a chiral ligand, giving the desired products with high enantioselectivity (up to 84% ee). Contrary to our previous studies, the electro-withdrawing character is not necessary for this reaction, i.e. the reaction of 3-methyl-(2-*N*-methylamino)pyridine proceeded (Scheme 29c).



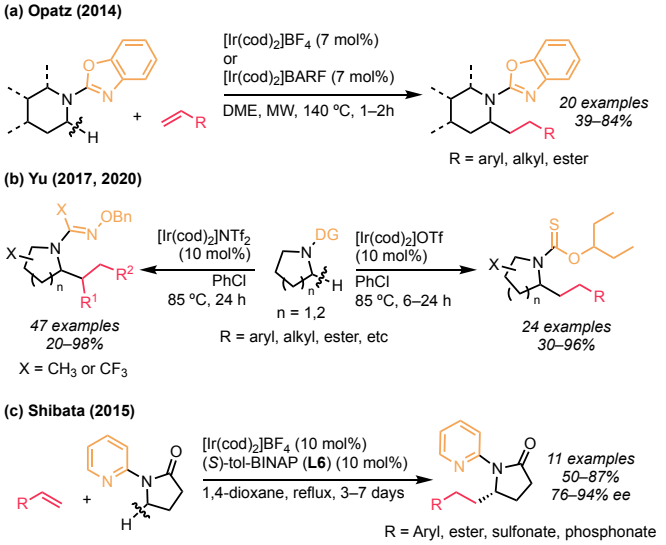
Scheme 29. Ir-catalysed cyclization of 2-(*N*-methyl)pyridines with α,ω-dienes



Scheme 30. Ir-catalysed urea-directed C(sp³)–H addition to alkenes

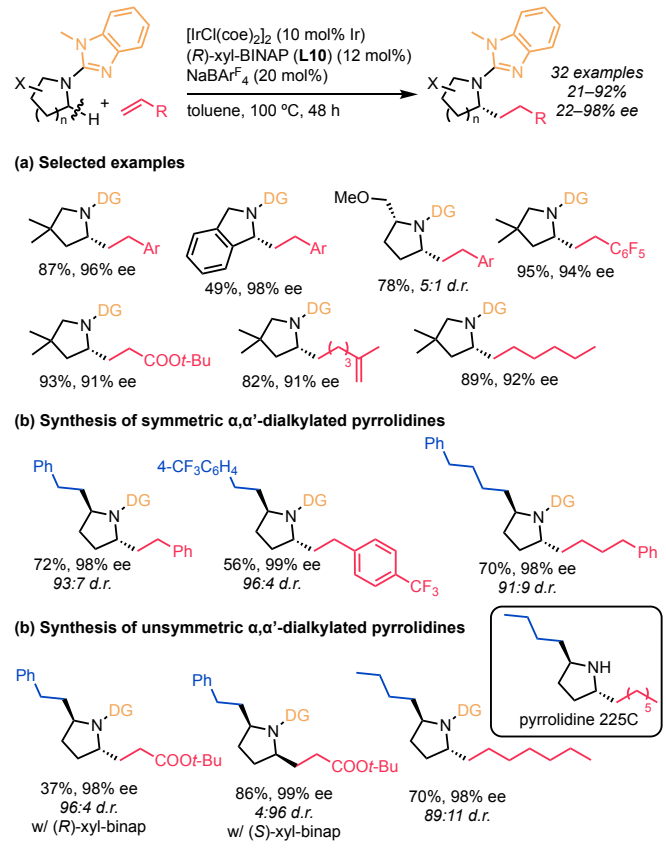
Our strategy for hydroarylation reactions catalysed by the neutral hydroxoiridium complex is characterised by the formation of an amidoiridium(I) species. In this respect, we found that ureas are suitable substrates for the formation of the amidoiridium species and subsequent C(sp³)–H activation (Scheme 30a).[63] The optimised conditions employed [Ir(OH)cod]$_2$ and 1,2-bis(diisopropylphosphino)benzene (dippbz, **L4**) and the corresponding alkylated products were obtained in high yields with a wide range of substrates. Styrenes, α-olefins, *N*-vinylamides, vinylsilane, vinyl ethers, vinyl phosphonate, acrylate, and diene were all tolerated up to the alkene scope, while arene- or alkyl-substituted ureas were applicable in the optimised reaction conditions. Unfortunately, however, the alkylation of methylene C–H bonds to the secondary or cyclic amine C–H bonds was not observed in this catalytic system. Deuterium-labelling experiments showed that C–H activation does not occur with the urea-type directing groups. In this context, the following year in 2018, we found that indolines are good substrates as secondary and cyclic alkylamines and for C(sp³)–H bond alkylation (Scheme 30b).[64] With the slight modifications in solvent concentration and ligand, the alkylation of indolines proceeded smoothly to give the alkylated products. Styrenes, α-olefins, and vinyl ethers were suitable for the reaction.

There have been several reports on iridium-catalysed C(sp³)–H alkylation of cyclic amines using the cationic iridium systems.[65] In 2014, Opatz and co-workers reported the α-alkylation of piperidines and tetrahydroisoquinolines with terminal alkenes in the presence of a cationic iridium catalyst, successfully using benzoxazole on the nitrogen as the directing group (Scheme 31a).[65a] Yu and co-workers developed the α-alkylation of 5- and 6-membered azacycles by designing the directing group (Scheme 31b).[65b,c] Thus, alkoxythiocarbonyl- and aldoxime-directed C(sp³)–H bond addition to a wide range of alkenes was achieved using the cationic iridium catalysts, and not only pyrrolidine but also piperidine, isoquinoline, and medicinally relevant azacycles were all tolerated for the reaction. Shibata and co-workers reported the alkylation of *N*-(2-pyridyl)-γ-butyrolactam (Scheme 31c).[65d] The cationic iridium catalyst ligating (*S*)-tol-BINAP (**L6**) catalysed the cross-coupling reaction of azacycles and styrenes or electron-deficient alkenes to give the α-alkylated γ-butyrolactam, which can be converted to γ- amino acids (76–94% ee). They also demonstrated the synthetic utility by the means of total synthesis of Pyrrolam A.

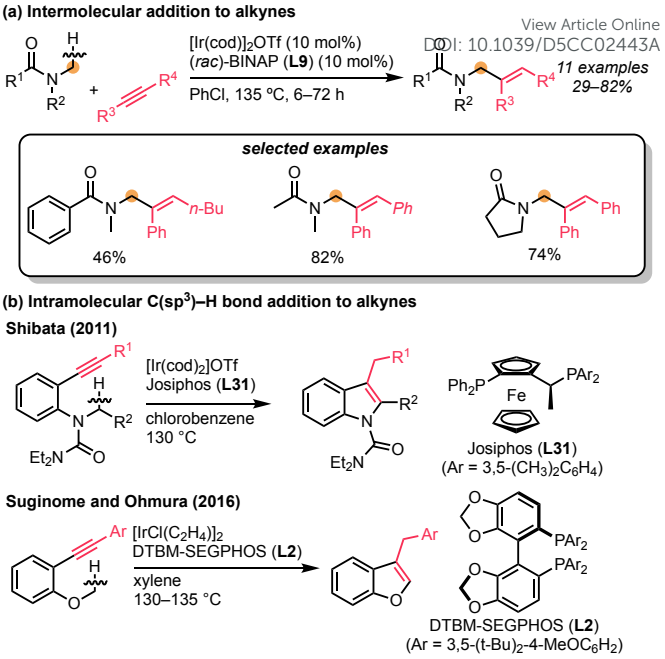


Scheme 31. Ir-catalysed C(sp³)–H alkylation of cyclic amines and lactam

The enantioselective alkylation of purely azacyclic compounds, such as pyrrolidines had not been achieved until our development in 2022 (Scheme 32).[66] We found that azole-type directing groups, such as benzimidazole, benzoxazole, and benzothiazole, were privileged structures to realise the enantioselective direct addition of the α-C(sp³)–H bond. Thus, the reaction of 5-membered cyclic amines bearing the *N*-methylbenzimidazole group with various alkenes, including styrenes, α-olefins, 1,5-diene, acrylate, and 1,1-disubstituted alkene, gave the α-chiral cyclic amines with generally high enantioselectivity (Scheme 32, 68–97% ee). The synthesis of symmetrical and unsymmetrical α,α'-dialkylated pyrrolidines was also achieved in a diastereo- and enantioselective manner (Scheme 27b, up to d.r = 96:4 and up to 99% ee). The synthesis of the analogue of pyrrolidine 225C, which is a trail pheromone of the pharaoh ant, *Monomorium pharaonis*, was also successful (Scheme 32c).



Scheme 32. Ir-catalysed enantioselective alkylation of cyclic amines



Scheme 33. Ir-catalysed C(sp3)–H bond addition to alkynes

Conclusion and Outlook

Transition metal-catalysed direct C–H bond functionalisation has become a streamlined and sustainable route for accessing valuable compounds from easily available chemicals. Recent advances in iridium catalysts for such molecular transformations can make the direct C–H bond functionalisation methodology more widely applicable. In this feature article, we have described our recent work on iridium-catalysed enantioselective C–H bond addition to the carbon–carbon double and triple bonds, including bicyclic alkenes, styrenes, vinyl ethers, α-olefins, and alkynes. Although not included in this feature article, there are also reports on enantioselective X–H bond addition, such as N-H bond addition (hydroamination)[67] C(sp)–H bond addition (hydroalkynylation),[68] and alkenyl C(sp²)–H bond addition.[69] Despite significant developments in iridium catalysts, there are still challenges regarding the range of substrates. For example, the enantioselective hydroarylation reaction is largely limited to monosubstituted alkenes, and the current catalytic system is less effective for more substituted alkenes. In this context, strategies involving directing groups or ligand tuning would provide a new approach to achieving highly regioselective and enantioselective hydroarylation.

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Another challenge lies in the dependence on the directing group. This limitation restricts the C–H activation site to the formation of thermodynamically stable five- or six-membered metallacycles, leaving more distal positions unreactive in current systems. Although directing-group-assisted C–H functionalisation has emerged as a powerful methodology for achieving site-selective reactions, the activation of C(sp^3)–H bonds still requires relatively strong directing groups, such as pyridyl. In contrast, the use of weakly coordinating directing groups, such as ketones, amides, esters, and alcohols, for C(sp^3)–H bond activation remains underdeveloped. A promising strategy to overcome this limitation would be the rational design of ligands for iridium complexes, analogous to strategies successfully employed in palladium-catalysed reactions.[2b,70]

Data availability

No new data is presented. References are made to the original work reviewed and summarised in this manuscript.

Conflicts of interest

There are no conflicts to declare

Acknowledgements

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References

1 (a) Z. Dong, Z. Ren, S. J. Thompson, Y. Xu and G. Dong, *Chem. Rev.*, 2017, ***117***, 9333. (b) T. Dalton, T. Faber and F. Glorius, *ACS Cent. Sci.* 2021, ***7***, 245. (c) W. Ali, G. A. Oliver, D. B. Werz and D. Maiti, *Chem. Soc. Rev.,* 2024, **53**, 9904.
2 (a) P. Gandeepan, T. Müller, D. Zell, G. Cera, S. Warratz and L. Ackermann, *Chem. Rev.*, 2019, ***119***, 2192. (b) S. K. Sinha, S. Guin, S. Maiti, J. P. Biswas, S. Porey and D. Maiti, *Chem. Rev.*, 2022, ***122***, 5682.
3 (a) C. G. Newton, S.-G. Wang, C. C. Oliveira and N. Cramer, *Chem. Rev.*, 2017, ***117***, 8908. (b) T. K. Achar, S. Maiti, S. Jana and D. Maiti, *ACS Catal.*, 2020, **10**, 13748. (c) W. Zeng, C. Han, S. Mohammed, S. Li, Y. Song, F. Sun and Y. Du, *RSC Med. Chem.*, 2024, ***15***, 788. (d) N. A. McGrath, M. Brichacek and J. T. Njardarson, *J. Chem. Educ.*, 2010, ***87***, 1348.
4 (a) G. Liao, T. Zhang, Z.-K. Lin and B.-F. Shi, *Angew. Chem., Int. Ed.* 2020, **59**, 19773. (b) J. M.-Roselló, A. G. Herraiz, B. Audic, A. Laverny and N. Cramer, *Angew. Chem., Int. Ed.* 2021, **60**, 13198.
5 (a) L. N. Lewis and J. F. Smith, *J. Am. Chem. Soc.*, 1986, **108**, 2728. (b) S. Murai, F. Kakiuchi, S. Sekine, Y. Tanaka, A. Kamatani, M. Sonoda, N. Chatani, *Nature*, 1993, **366**, 529.
6 (a) Ł. Woźniak, J.-F. Tan, Q.-H. Nguyen, A. M. du Vigné, V. Smal, Y.-X. Cao and N. Cramer, *Chem. Rev.*, 2020, **120**, 10516. (b) I. F. Yu, J. W. Wilson and J. F. Hartwig, *Chem. Rev.*, 2023, **123**, 11619. (c) J. Zhu, Y. Wang, A. D. Charlack and Y.-M. Wang, *J. Am. Chem. Soc.,* 2022, **144**, 15480. (d) Z. Liu, Z.-J. Shi, L. Liu, M. Zhang, M.-C. Zhang, H.-Y. Guo and X.-C. Wang, *J. Am. Chem. Soc.*, 2023, **145**, 11789.
7 T. Ziegler, V. Tschinke and A. Becke, *J. Am. Chem. Soc.*, 1987, **109**, 1351.
8 C. Takashima, H. Kurita, H. Takano, Y. Ikabata, T. Shibata and H. Nakai, *J. Phys. Chem. A*, 2022*,* **126***,* 7627.
9 C. Zhao, Q. Ge, B. Wang and X. Xu, *Org. Chem. Front.*, 2017, **4**, 2327.
10 (a) S. Pan and T. Shibata, *ACS Catal.,* 2013, **3**, 704. (b) D. F. Fernández, J. L. Mascareñas and F. López, *Chem. Soc. Rev.*, 2020, **49**, 7378.
11 T. Nishimura, *Chem. Rec.*, 2021, **21**, 3532.
12 a) R. Aufdenblatten, S.Diezi and A. Togni, *Monatsh. Chem.*, 2000, **131**, 1345. b) R. Dorta and A. Togni, *Chem. Commun.*, 2003, 760.
13 K. Tsuchikama, M. Kasagawa, Y. Hashimoto, K. Endo and T. Shibata, *J. Organomet. Chem.*, 2008, ***693***, 3939.
14 C. S. Sevov and J. F. Hartwig, *J. Am. Chem. Soc.*, 2013, ***135***, 2116.
15 (a) T. Shirai and Y. Yamamoto, *Angew. Chem., Int. Ed.*, 2015, ***54***, 9894. (b) T. Shirai, T. Okamoto and Y. Yamamoto, *Asian J. Org. Chem.*, 2018, ***7***, 1054.
16 M. Nagamoto, J. Fukuda, M. Hatano, H. Yorimitsu and T. Nishimura, *Org. Lett.*, 2017, ***19***, 5952.
17 A. R.-Arenas, V. Hornillos, J. I.-Sigüenza, R. Fernández, J. L.-Serrano, A. Ros and J. M. Lassaletta, *J. Am. Chem. Soc.*, 2020, ***142***, 2628.
18 X. Hu, Y. Zhao, T. He, C. Niu, F. Liu, W. Jia, Y. Mu, X. Li and Z.-Q. Rong, *Chem. Sci.*, 2024, ***15***, 13541.
19 T. P. Aldhous,R. W. M. Chung, A. G. Dalling and J. F. Bower, *Synthesis* 2021, ***53***, 2961.
20 S. Pan, N. Ryu and T. Shibata, *J. Am. Chem. Soc.*, 2012, ***134***, 17474.
21 K. Yamakawa and T. Nishimura, *Adv. Synth. Catal.*, 2023, ***365***, 2013.
22 K. Yamakawa and T. Nishimura, *ACS Catal.*, 2025, ***15***, 8737.
23 T. P. Aldhous, R. Chung, A. Hassan, A. G. Dalling, P. Cooper, S. Grélaud, R. J. Mudd, L. J. Feron, P. D. Kemmitt and J. F. Bower, *Angew. Chem., Int. Ed.* ***2025***, e202502569.
24 C. M. Filloux and T. Rovis, *J. Am. Chem. Soc.,* 2015, ***137***, 508.
25 K. Yamakawa, I. Nakamura, K. Sakamoto and T. Nishimura, *J. Org. Chem.*, 2023, ***88***, 7858.
26 G. E. M. Crisenza, N. G. McCreanor and J. F. Bower, *J. Am. Chem. Soc.*, 2014, ***136***, 10258.
27 G. Huang and P. Liu, *ACS Catal.*, 2016, ***6***, 809.
28 (a) G. E. M. Crisenza, O. O. Sokolova and J. F. Bower, *Angew. Chem., Int. Ed.* 2015, ***54***, 14866. (b) P. Cooper, A. G. Dalling, E. H. E. Farrar, T. P. Aldhous, S. Grélaud, E. Lester, L. J. Feron, P. D. Kemmitt, M. N. Grayson and J. F. Bower, *Chem. Sci.*, 2022, ***13***, 11183.
29 S. Grélaud, P. Cooper, L. J. Feron and J. F. Bower, *J. Am. Chem. Soc.*, 2018, ***140***, 9351.
30 Y. Ebe and T. Nishimura, *J. Am. Chem. Soc.*, 2015, ***137***, 5899.
31 M. Hatano, Y. Ebe, T. Nishimura and H. Yorimitsu, *J. Am. Chem. Soc.*, 2016, ***138***, 4010.
32 K. Murakami, K. Sakamoto and T. Nishimura, *Synthesis*, 2022, ***54***, 4753.
33 D. Yamauchi, T. Nishimura and H. Yorimitsu, *Chem. Commun.*, 2017, ***53***, 2760.
34 D. Fiorito, S. Scaringi and C. Mazet, *Chem. Soc. Rev.*, 2021, ***50***, 1391.
35 (a) Y. Ebe, M. Onoda, T. Nishimura and H. Yorimitsu, *Angew. Chem., Int. Ed.* 2017, ***56***, 5607. (b) K. Sakamoto and T. Nishimura, *Adv. Synth. Catal.* 2019, ***361***, 2124.

36 (a) K. H. N. Tang, K. Uchida, K. Nishihara, M. Ito and Takanori Shibata, *Org. Lett.*, 2022, **24**, 1313. (b) K. H. N. Tang, R. Tokutake, M. Ito and Takanori Shibata, *Org. Lett.*, 2023, **25**, 5197. (c) F. Li, Y. Luo, J. Ren, Q. Yuan, D. Yan and W. Zhang, *Angew. Chem., Int. Ed.* 2023, **62**, e202309859. (d) K. H. N. Tang, H. Takahashi, R. Tokutake and T. Shibata. *Adv. Synth. Catal.* 2024, **366**, 3610.
37 M. Zhanga and G. Huang, *Dalton Trans.*, 2016, **45**, 3552.
38 X.-Y. Gou, X.-Y. Zhu, B.-S. Zhang and Y.-M. Liang, *Chem. Eur. J.* 2023, **29**, e202203351.
39 S. Vijayasaradhi and I. S. Aidhen, *Org. Lett.*, 2002, **10**, 1739.
40 K. Sakamoto, M. Nagai, Y. Ebe, H. Yorimitsu and T. Nishimura, *ACS Catal.* 2019, **9**, 1347.
41 (a) C. Yu, Y. Liu, X. Xie, S. Hu, S. Zhang, M. Zeng, D. Zhang, J. Wang and H. Liua, Adv. Synth. Catal. 2021, 363, 4926 *Adv. Synth. Catal.*, 2021, **363**, 4926. (b) W. Zhu, Q. Sun, H. Chang, H.-X. Zhang, Q. Wang, G. Chen and G. He, *Chin. J. Chem.*, 2022, **40**, 571.
42 (a) S. Pan, N. Ryu and T. Shibata, *Adv. Synth. Catal.*, 2014, **356**, 929. (b) T. Shibata and H. Takano, *Org. Chem. Front.*, 2015, **2**, 383. (c) T. Shibata, M. Michino, H. Kurita, Y. Tahara and K. S. Kanyiva, *Chem. Eur. J.*, 2017, **23**, 88. (d) T. Shibata, H. Kurita, S. Onoda and K. S. Kanyiva, *Asian J. Org. Chem.*, 2018, **7**, 1411. (e) T. Shibata, M. Sasaki, M. Kojima and M. Ito, *Org. Lett.*, 2021, **23**, 9078.
43 R. K. Thalji, J. A. Ellman and R. G. Bergman, *J. Am. Chem. Soc.*, 2004, **126**, 7192.
44 T. Shibata, N. Ryu and H. Takano, *Adv. Synth. Catal.*, 2015, **357**, 1131.
45 V. S. Shinde, M. V. Mane, L. Cavallo and M. Rueping, *Chem. Eur. J.*, 2020, **26**, 8308.
46 K. Sakamoto and T. Nishimura, *Org. Biomol. Chem.*, 2021, **19**, 684.
47 (a) T. Ohmura, S. Kusaka and M. Suginome, *Chem. Commun.*, 2021, **57**, 13542. (b) S. Kusaka, T. Ohmura and M. Suginome, *Chem. Lett.*, 2022, **51**, 601.
48 A. Arribas, M. Calvelo, D. F. Fernández, C. A. B. Rodrigues, J. L. Mascareñas and F. López, *Angew. Chem., Int. Ed.* 2021, **60**, 19297.
49 A. Arribas, M. Calvelo, A. Rey, J. L. Mascareñas and F. López, *Angew. Chem., Int. Ed.* 2024, **63**, e202408258.
50 C. He, W. G. Whitehurst and M. J. Gaunt, *Chem*, 2019, **5**, 1031.
51 For selected early examples, see; (a) N. Chatani, T. Asaumi, S. Yorimitsu, T. Ikeda, F. Kakiuchi and S. Murai, *J. Am. Chem. Soc.*, 2001, **123**, 10935. (b) S. D. Bergman, T. E. Storr, H. Prokopcov, K. Aelvoet, G. Diels, L. Meerpoel and B. U. W. Maes, *Chem. Eur. J.*, 2012, **18**, 10393. (c) M. Schinkel, L. Wang, K. Bielefeld and L. Ackermann, *Org. Lett.*, 2014, **16**, 1876.
52 R. C. DiPucchio, S.-C. Rosca and Laurel L. Schafer, *J. Am. Chem. Soc.*, 2022, **144**, 11459.
53 C. -H. Jun, D. -C. Hwang and S. -J. Na, *Chem. Commun.*, 1998, 1405.
54 B. DeBoef, S. J. Pastine and D. Sames, *J. Am. Chem. Soc.*, 2004, **126**, 6556.
55 (a) S. Pan, K. Endo and T. Shibata, *Org. Lett.*, 2011, **17**, 4692. (b) S. Pan, Y. Matsuo, K. End and T. Shibata, *Tetrahedron*, 2012, **68**, 9009.
56 M. Nagai, M. Nagamoto, T. Nishimura and H Yorimitsu, *Chem. Lett.*, 2017, **46**, 1176.
57 H. Hattori and T. Nishimura, *Adv. Synth. Catal.*, 2018, **360**, 4827.
58 (a) T. Torigoe, T. Ohmura and M. Suginome, *Angew. Chem., Int. Ed.* 2017, **56**, 14272. (b) T. Ohmura, S. Kusaka, T. Torigoe and M. Suginome, *Adv. Synth. Catal.*, 2019, **361**, 4448.
59 (a) T. Ohmura, K. Yagi, S. Kusaka and M. Suginome, *ACS Catal.*, 2020, **10**, 3152. (b) K. Yagi, T. Ohmura and M. Suginome, *ACS Catal.*, 2024, **14**, 2014.
60 D. Yamauchi, I. Nakamura and T. Nishimura, *Chem. Commun.*, 2021, **57**, 11787.
61 K. Sakamoto and T. Nishimura, *Chem. Commun.*, 2022, **58**, 11783.
62 K. Tanaka, H. Hattori, R. Yabe and T. Nishimura, *Chem. Commun.*, 2022, **58**, 5371.
63 D. Yamauchi, T. Nishimura and H. Yorimitsu, *Angew. Chem., Int. Ed.*, 2017, **56**, 7200.
64 I. Nakamura, D. Yamauchi and T. Nishimura, *Asian J. Org. Chem.*, 2018, **7**, 1347.
65 (a) G. Lahm and T. Opatz, *Org. Lett.*, 2014, **16**, 4201. (b) A. T. Tran and J.-Q. Yu, *Angew. Chem., Int. Ed.* 2017, **56**, 10530. (c) P. Verma, J. M. Richter, N. Chekshin, J. X. Qiao and J.-Q. Yu, *J. Am. Chem. Soc.*, 2020, **142**, 5117. (d) Y. Tahara, M. Michino, M. Ito, K. S. Kanyiva and T. Shibata, *Chem. Commun.*, 2015, **51**, 16660.
66 D. Yamauchi, K. Yamakawa and T. Nishimura, *Org. Lett.*, 2022, **24**, 6828.
67 (a) S. Pan, K. Endo and T. Shibata, *Org. Lett.*, 2012, **14**, 780. (b) Y. Xi, S. Ma and J. F. Hartwig, *Nature*, 2020, **588**, 254. (c) K. Yamakawa, K. Sakamoto and T. Nishimura, *Chem. Commun.*, 2023, **59**, 12871. (d) Y.-W. Sun, X. Sun, H.-T. Tan and B.-J. Li, *Angew. Chem., Int. Ed.* 2025, e202422944.
68 (a) Z.-X. Wang and B.-J. Li, *J. Am. Chem. Soc.*, 2019, **23**, 9312. (b) S.-L. Zhang, W.-W. Zhang and B.-J. Li, *J. Am. Chem. Soc.*, 2021, **25**, 9639. (c) Z.-X. Wang, P.-C. Gao, E.-Z. Lin, B.-J. Li, *Angew. Chem., Int. Ed.* 2022, **61**, e202200075.
69 (a) D. F. FernáLndez, M. Gulías, J. L. Mascareñas and F. López, *Angew. Chem., Int. Ed.*, 2017, **56**, 9541. (b) K. Murakami, M. Nagamoto and T. Nishimura, *Chem. Lett.*, 2020, **49**, 732. (c) X. Sun, E.-Z. Lin and B.-J. Li, *J. Am. Chem. Soc.*, 2022, **144**, 17351. (d) F. Hong, C. M. Robertson and J. F. Bower, *J. Am. Chem. Soc.*, 2024, **146**, 22923.
70 J. He, M. Wasa, K. S. L. Chan, Q. Shao and J.-Q. Yu, *Chem. Rev.*, 2017, **117**, 8754.

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No new data is presented. References are made to the original work reviewed and summarised in this manuscript.