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# Recent development in transition metal-catalysed C–H olefination†

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Transition metal-catalysed functionalizations of inert C–H bonds to construct C–C bonds represent an ideal route in the synthesis of valuable organic molecules. Fine tuning of directing groups, catalysts and ligands has played a crucial role in selective C–H bond ($sp^2$ or $sp^3$) activation. Recent developments in these areas have assured a high level of regioselectivity in C–H olefination reactions. In this review, we have summarized the recent progress in the oxidative olefination of $sp^2$ and $sp^3$ C–H bonds with special emphasis on distal, atroposelective, non-directed $sp^2$ and directed $sp^3$ C–H olefination. The scope, limitation, and mechanism of various transition metal-catalysed olefination reactions have been described briefly.

## 1. Introduction

Transition metal-catalysed C–H bond activations have emerged as an important tool in synthetic organic chemistry for the construction of C–C bonds in a more economical fashion.[1] In the last few decades, significant developments have been observed towards sustainable organic transformations by researchers all over the world.[2] In this regard, transition metal-catalysed C–H olefination received special attention due to the versatility of olefinated compounds in many valuable products (Fig. 1). Vinyl arenes act as key intermediates in many organic transformations and are also present in numerous bioactive compounds.[3–5] Pd-catalysed Mizoroki–Heck cross-coupling (Nobel Prize in 2010) of arene electrophiles with alkenes has emerged as an alternative route to the conventional olefination reactions.[6] Direct oxidative C–H olefination with alkenes known as the Fujiwara–Moritani reaction represents an advanced version of Mizoroki–Heck couplings as it avoids prefunctionalized starting compounds.[7] However, poor regioselectivity, low catalyst efficiency and usage of excess arenes (solvent amount) limits the Fujiwara–Moritani reaction and prompted the development of more efficient approaches. The foremost challenge in C–H activation is to selectively functionalize a particular C–H bond in the presence of several electronically equivalent C–H bonds. To overcome this issue, usage of directing groups has come up as one of the most reliable approaches. Directing groups concentrate metals in the close proximity of the desired C–H bond to be functionalized and thus improve the selectivity and reactivity. The field of directed

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† Dedicated to Prof. Wolfgang Kaim on the occasion of his 70th birthday.

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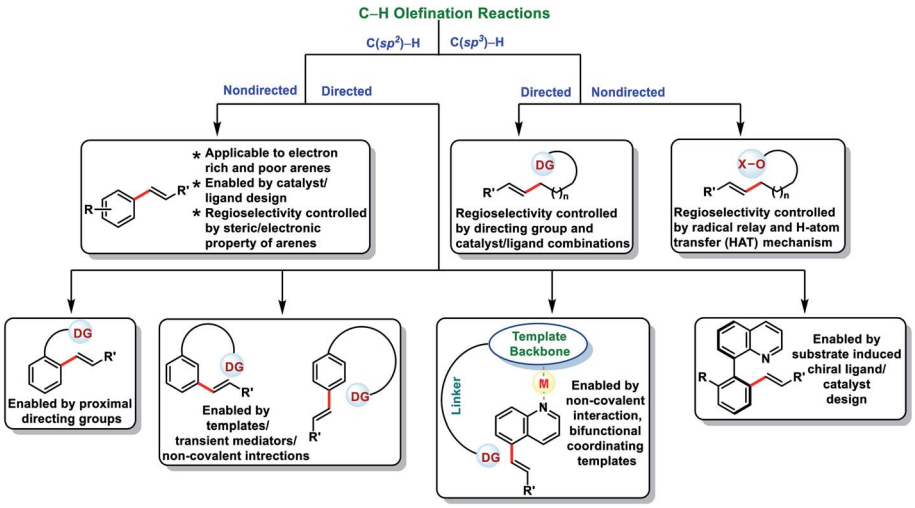


Fig. 1 Direct C–H olefination reactions.

C–H bond activations has grown tremendously and many chelating groups have been explored that can serve as the auxiliaries. Furthermore, by understanding the distal and geometrical relationships between the functional group and targeted C–H bond, U- and D-shaped templates, transient mediators and non-covalent interactions were discovered to activate *meta*, *para* and other distal C–H bonds.[8]

Direct olefination of the relatively unreactive C(sp$^3$)–H bond represents one of the most fascinating and advance strategies in synthetic organic chemistry. However, in contrast to the C(sp$^2$)–H bond, functionalization of the C(sp$^3$)–H bond, particularly olefination, is not well investigated and limited reports are available in the literature. Selective functionalisation of the C(sp$^3$)–H bond is much more difficult due to the lack of the assistance of the π-group, which could efficiently interact with the transition-metal centre. However, the last few decades witnessed an upsurge in distal C(sp$^3$)–H olefination by installing the directing group as well as through the radical translocation strategy (Fig. 2).[9]

In this review, we have summarized the progress in oxidative C–H olefination reactions until summer 2020 with special emphasis on the distal, atroposelective, non-directed C(sp$^2$)–H and directed C(sp$^3$)–H olefinations. Also, advancements in *ortho*-C(sp$^2$)–H olefination from 2017 have been discussed here.[2a,b,e,f]

## 2. Proximal C(sp$^2$)–H olefination

### 2.1. *Ortho*-C(sp$^2$)–H olefination

In 2017, Garcia and co-workers reported a Pd-catalysed *ortho*-C–H olefination of 2-phenylethylamines **1** with activated alkenes. In the reaction, a primary amine acted as the directing group which followed an intramolecular aza-Michael addition route for the construction of 3,3-disubstituted tetrahydroisoquinolines **2** (Scheme 1).[10] A bidentate silver salt such as a carbonate or an acetate was found to be indispensable for the reaction. The strategy was compatible with 1,1-disubstituted-2-phenylethylamine substrates only.

Wang's group disclosed the Pd-catalysed *N*-Ac-Leu-OH ligand-controlled enantioselective C–H olefination of racemic sulfoxides **3** to construct chiral diaryl sulfoxides **4** in moderate yield and excellent enantioselectivity (up to 99% ee) (Scheme 2).[11] Symmetric and nonsymmetric sulfoxides were

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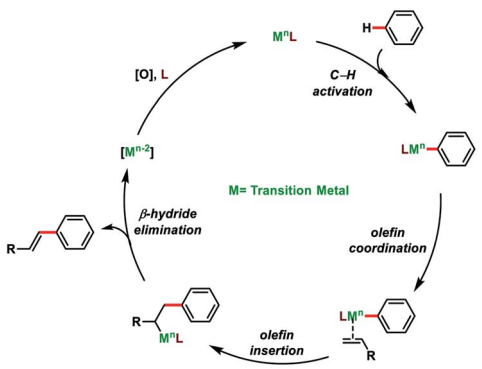
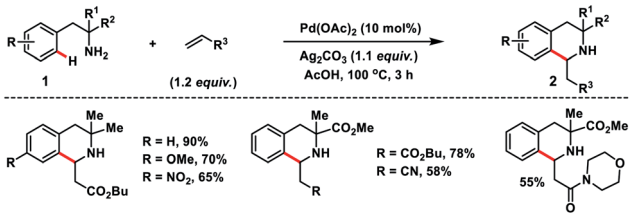
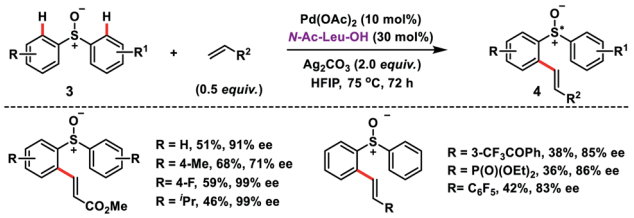



Fig. 2 General mechanism for direct C–H olefination reactions.



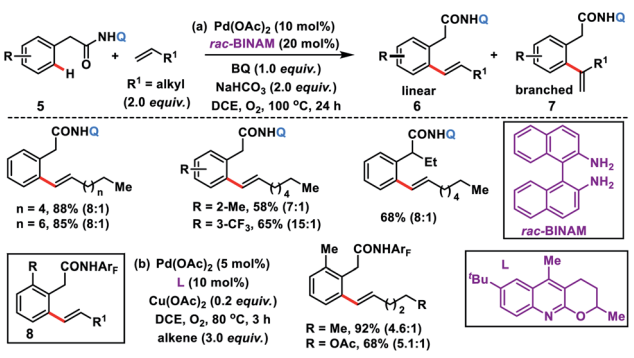

Scheme 1 Primary amine-directed *ortho*-C(sp$^2$)–H olefination.



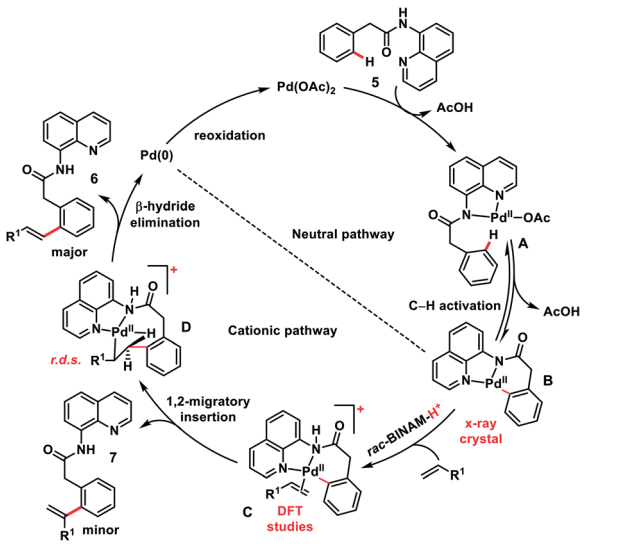

Scheme 2 Pd-catalysed enantioselective C–H olefination of diaryl sulfoxides.

functionalized through desymmetrization and parallel kinetic resolution (PKR). Olefination of the (*S*)-isomer occurred at the *para*-substituted benzene ring while for the (*R*)-isomer olefination took place at the other phenyl ring with high ee. It indicated that regiodivergent parallel kinetic resolution (PKR) was involved in the reaction. The enantioselectivity in the transformation was induced during the Pd(II)/*N*-Ac-Leu-OH-catalysed asymmetric C–H activation step.

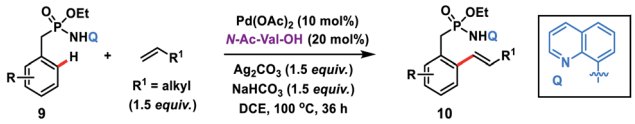
The use of unbiased aliphatic alkenes for the *ortho*-olefination of phenyl acetic acids **5** in high regio- and stereoselectivity was first reported by our group (Scheme 3a).[12a] In this Pd-catalysed olefination reaction a bidentate directing group 8-aminoquinoline was found to be the suitable auxiliary as it provided rigid coordination to Pd and formed a stable six-membered palladacycle during C–H activation. The reaction provided better yield and selectivity in the presence of the ligand *rac*-BINAM as it saturates the coordination site of the palladium. A library of terminal aliphatic alkenes irrespective of their chain length and functional group were well suited under the reaction conditions and provided olefinated products **6** in good yield and selectivity for linear/branched products. Several phenyl acetic acid derivatives including the commercial drug ibuprofen were olefinated efficiently. Sequential diolefination of phenyl acetic acid with two different alkenes indicated that the catalytic system used is very reactive and efficient. Similarly, Dai, Yu and co-workers also presented a Pd(II)-catalysed *ortho*-C(sp$^2$)–H olefination of phenylacetic acid derivatives with unactivated aliphatic alkenes in 2018 (Scheme 3b).[12b] They found that a quinoline based ligand was crucial for the purpose whereas the monodentate amide coordinating group was used as a weak directing group. In the transformation, both simple and functionalized aliphatic alkenes were compatible with different acids and provided β-alkylated styrenes **8** in good yield. To make the protocol more convenient molecular oxygen was utilized as a terminal oxidant along with a catalytic copper salt as the co-oxidant. Detailed experimental and computational studies were carried out by our group to understand the origins of the selectivity.[12c] A series of experiments such as reaction rate and order determination, control experiments, isotopic labelling and Hammett analysis were performed to understand the reaction mechanism. NMR and kinetic studies using aryl-palladium intermediates helped to understand the arene C–H activation, olefin coordination and carbopalladation steps. KIE experiments revealed that the C–H activation step was not involved in the rate limiting step instead β-hydride elimination was controlling the overall catalytic process. The results of various control experiments were supported by DFT studies and revealed the origin of regio and stereoselectivity. The findings of experimental and computational studies suggested that the overall mechanism combines neutral and cationic pathways (Scheme 4). A neutral aryl-palladium intermediate **B** was formed by the fast and reversible C–H activation. Coordination of the unactivated olefin to the neutral aryl-palladium species was possible, however for efficient reactivity a positively charged intermediate **C** was required. Intermediate **C** underwent




Scheme 3 Pd-catalysed aryl C–H olefination with unbiased aliphatic alkenes.




Scheme 4 Plausible mechanism for C–H olefination of phenylacetic amides.

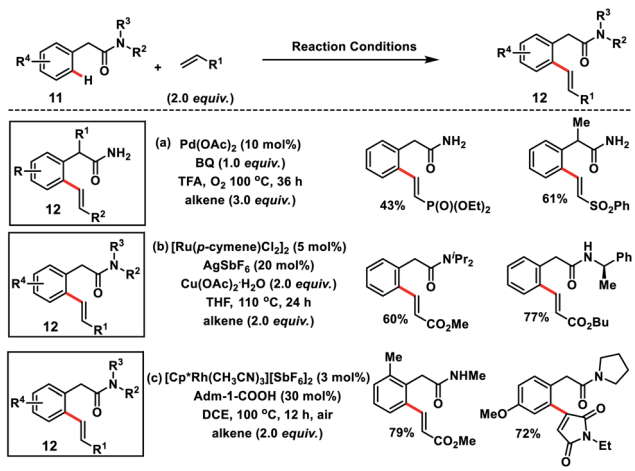



Scheme 5 Pd(II)-catalysed olefination of benzyl phosphonamide.

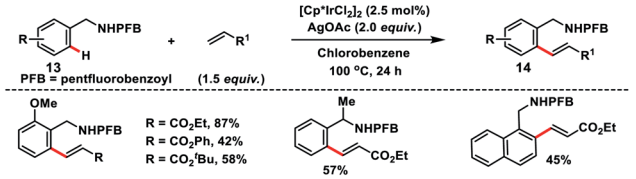
migratory insertion with an olefin to form intermediate **D** followed by β-hydride elimination to form the kinetically and thermodynamically favoured linear olefinated product **6**. Our group further expanded the application of unbiased aliphatic alkenes for the *ortho* C–H olefination of benzyl phosphonamides **9** (Scheme 5).[12d] The strategy was well suited for various benzyl phosphonamides and aliphatic alkenes to afford linear olefinated products **10** in good yield and selectivity.

Loh and co-workers reported Pd-catalysed *ortho*-olefination of *O*-acetyl cyanohydrins aided by the synergetic directing effect of acetoxy and cyano functionalities.[13] They used a mono-N-protected amino acid (MPAA), *N*-Ac-Gly-OH ligand, and $Ag_2CO_3$ oxidant to perform the reaction which was well suited with a variety of substrates and offered the anticipated products in good yield with high regioselectivity.

Amit and co-workers succeeded in the olefination of arylacetamides **11** using abundant and easily manipulatable primary amides as the effective directing group (Scheme 6a).[14a] They used benzoquinone along with oxygen as the oxidant. A series of alkenes were installed at the *ortho*-position of arylacetamide derivatives in moderate to good yields **12** with high regio and diastereoselectivity. Ackermann and co-workers in 2018 demonstrated the Ru(II)-catalysed *ortho*-C($sp^2$)–H olefination of weakly *O*-coordinating arylacetamides *via* a less favourable six-membered ruthenacycle (Scheme 6b).[14b] The strategy supports various substituted tertiary, secondary and even challenging primary amides and provided substituted olefins **12** in a chemo-, regio- and stereoselective manner. DFT studies showed that a six-membered ruthenacycle was formed *via* carboxylate mediated base-assisted internal electrophilic-type substitution (BIES) of the C–H bond and migratory insertion of an alkene




Scheme 6 Amide-directed *ortho*-C($sp^2$)–H olefination.



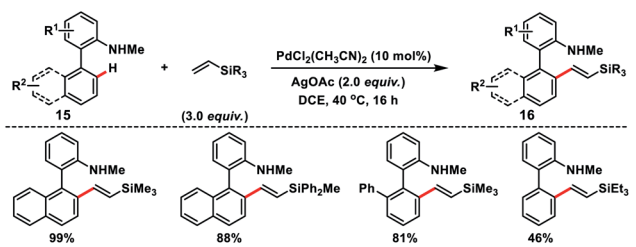

Scheme 7 Pentafluoro benzoyl-directed olefination of benzylamine.

involved in the rate-limiting step. Jeganmohan's group in 2019 utilized a Rh(III)-catalyst for the similar oxidative olefination of arylacetamides **11** with activated alkenes in good to excellent yields (Scheme 6c).[14c] Atmospheric oxygen served as the sole oxidant to regenerate the catalyst. A range of substituted arylacetamides underwent oxidative coupling with various acrylates and maleimides to furnish olefinated products **12** in a highly regio and diastereoselective manner. Weak coordination of acetamide oxygen with Rh directed it towards *ortho*-metalation *via* deprotonation to form a six-membered metalacyclic intermediate similar to the Ru-catalyst.

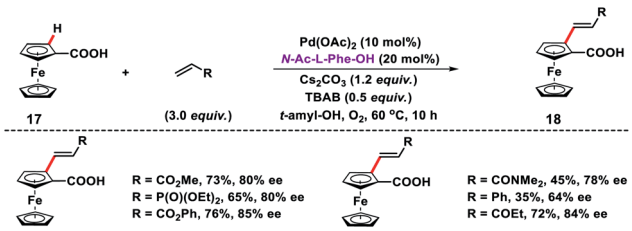
Ir-catalysed *ortho*-C($sp^2$)–H olefination of benzylamines **13** with acrylates was reported by Fu and co-workers using pentafluoro benzoyl (PFB) as the new directing scaffold (Scheme 7).[15] The reaction proceeded well with a series of substituted benzylamines in the presence of AgOAc oxidant and provided mono-olefinated products **14** in good yields. The reaction proceeded through the activation of the catalyst by AgOAc followed by the *ortho*-C–H bond activation *via* a concerted metalation–deprotonation (CMD) pathway resulting in a metallacycle. Insertion of an alkene tracked by β-hydride elimination yielded an olefinated product and Ir(I) species, which was re-oxidized to Ir(III) by AgOAc.

Cui and co-workers reported an interesting Pd-catalysed amino-chelation-assisted olefination of arenes **15** with an unactivated vinylsilane (Scheme 8).[16] They developed a ligand-free approach to synthesize a library of arylated vinylsilanes **16** in good to excellent yield with (*E*)-selectivity. It was interesting to note that the geometry of the product was controlled by the directing group, since biaryl carboxylic acids under similar conditions provided olefinated products but in poor *E*/*Z* ratios.

Acid directed olefination of ferrocene carboxylic acid **17** has been developed by Wu and co-workers to synthesize 1,2-disubstituted ferrocene carboxylic acids **18** with planar chirality using the chiral MPAA ligand *N*-Ac-L-Phe-OH (Scheme 9).[17] Diverse alkenes such as acrylates, acrylamides, vinyl phosphates, vinyl




Scheme 8 C($sp^2$)–H olefinations of 2-amino biaryls with vinylsilanes.



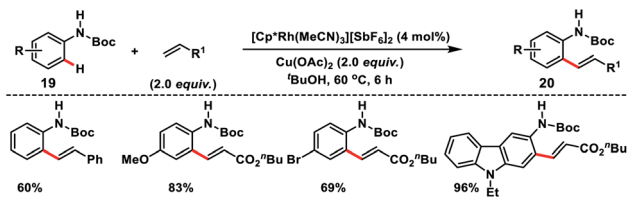

Scheme 9 Enantioselective C(sp$^2$)–H olefinations of ferrocene carboxylic acid.

ketones and styrenes were tolerated under the given reaction conditions. Ferrocenium ion was formed in the presence of oxygen and served as the terminal oxidant to regenerate Pd(II) from Pd(0).

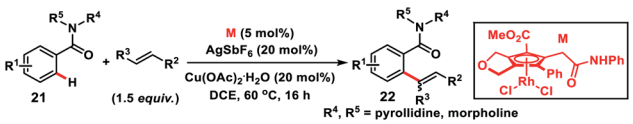
Mahiuddin's group further explored the directing group and used carboxylate as a weak directing group in Ru(II)-catalysed *ortho*-C(sp$^2$)–H olefination of aromatic carboxylic acids with styrenes.[18] The weak coordination of acid functionality serving as directing group even in the presence of the strong coordinating acetamide functional group under the reaction conditions.

Satoh, Miura and co-workers in 2017 developed a Rh(III)-catalysed *N*-Boc directed *ortho*-olefination of anilines **19** with alkenes using a copper salt oxidant (Scheme 10).[19] A series of alkenes such as acrylates, acrylamides, acrylonitrile and styrenes reacted with different anilines to afford corresponding *ortho*-olefinated products **20** in good yield. Styrene reacted slightly at elevated temperature and high catalyst loading. The *ortho*-olefinated anilines could be further derivatized into valuable nitrogen-containing heterocycles such as indoles and quinolines.

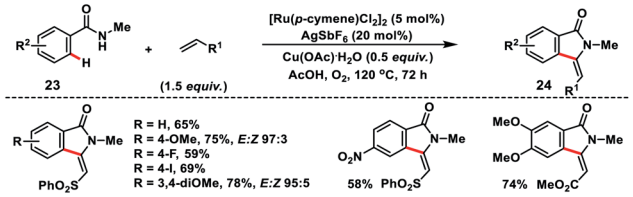
Shibata, Tanaka and co-workers in 2019 synthesized a moderately electron-deficient cyclopentadienyl Rh(III)-complex. The Rh(III)-complex bearing an ester and pendant amide moieties on the Cp ring was used for the aerobic oxidative olefination of benzamides **21** with styrene derivatives (Scheme 11).[20a] Diverse alkenes reacted with a multitude of benzamides to deliver corresponding products **22** in good yield. The ester moiety accelerates cleavage of the C–H bond and olefin insertion by reducing the electron density on the Rh-centre while the secondary amide eased C–H bond cleavage by intramolecular C–H extraction. Recently, Tanaka and co-workers came up with another highly active unsubstituted cyclopentadienyl rhodium(III)-complex for the oxidative *ortho*-olefination of sterically demanding amides.[20b]




Scheme 10 Rh-catalysed *N*-Boc-directed *ortho*-olefinations of anilines.




Scheme 11 Modified Rh(III)-catalysed *ortho*-olefination of amides.

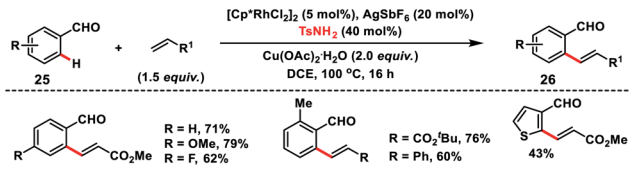



Scheme 12 Ru(II)-catalysed cyclisation of benzamides with activated alkenes.

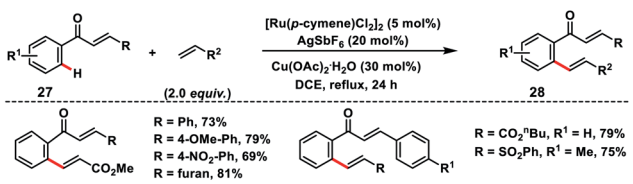
Jeganmohan and co-workers established a Ru(II)-catalysed oxidative olefination followed by the intramolecular cyclisation of benzamides **23** with vinyl sulfone for the synthesis of 3-methyleneisoindolin-1-ones **24** in good yields and *E*/*Z* ratio (Scheme 12).[21] Furthermore, they applied the oxidative cyclisation of benzamide for the total synthesis of aristolactam alkaloids.

Rhodium(III)-catalysed *ortho*-C(sp$^2$)–H olefination of aldehydes **25** was developed by Wang and co-workers in 2017 with the use of $TsNH_2$ as a transient directing group (Scheme 13).[22] The *in situ* generated imine formed *via* condensation of aldehyde and amine served as the directing group for the olefination of a variety of aldehydes with olefins and provided products **26** in good yield. KIE experiments suggest that cleavage of the C–H bond was involved in the rate determining step.

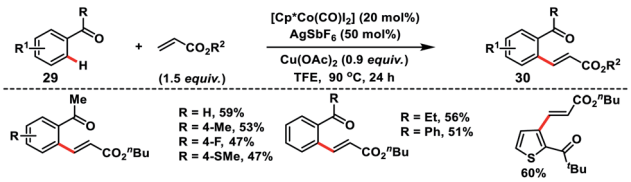
Ru(II)-catalysed enone carbonyl directed *ortho*-C(sp$^2$)–H olefination of chalcones **27** was developed by Bakthadoss and co-workers in 2018 using hydrated $Cu(OAc)_2$ as the oxidant (Scheme 14).[23] A variety of activated olefins coupled with




Scheme 13 Transient-directed *ortho*-C(sp$^2$)–H olefinations of aldehydes.




Scheme 14 Ru(II)-catalysed enone carbonyl-directed olefination of chalcones.



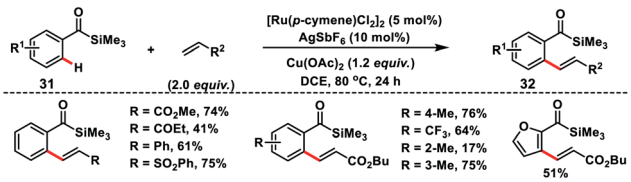

Scheme 15 Co(III)-catalysed *ortho*-olefination of aromatic ketones.

chalcone derivatives and afforded olefinated products **28** in high yield and stereoselectivity. In 2018, Ir-catalysed *ortho*-C($sp^2$)–H olefination of aromatic systems was demonstrated by Elumalai and co-workers employing diverse directing groups bearing the carbonyl functionality.[24] The oxidative olefination reaction proceeded smoothly in the presence of an external oxidant $Cu(OAc)_2$ and additive $AgPF_6$ to provide corresponding products in good yield.

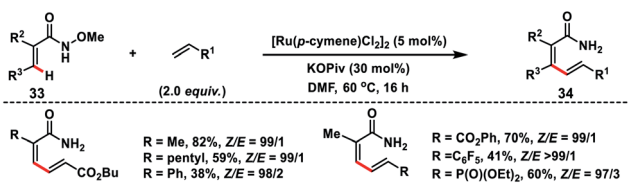
Co-catalysed olefination of aromatic ketones **29** with the assistance of the weakly coordinating carbonyl group was discussed by Maji and co-workers (Scheme 15).[25] A wide range of aromatic and heteroaromatic ketones irrespective of the electronic properties coupled with activated olefins to produce olefinated products **30** in good yield and *E*-selectivity.

The easily manipulative acylsilane as the directing group for Ru(II)-catalysed oxidative olefination of aroylsilanes **31** with alkenes was demonstrated by Zhang and co-workers (Scheme 16).[26] They utilized a copper salt as an external oxidant and the reaction was applicable to a broad range of aroylsilanes including heterocycles. Aroylsilanes coupled with a variety of alkenes and delivered *ortho*-olefinated products **32** in good yield with excellent regio and stereoselectivity.

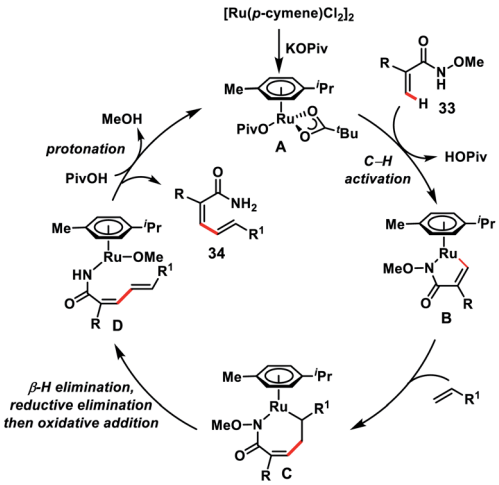
Zhong's group in 2017 demonstrated a Ru-catalysed olefination reaction at relatively difficult alkenyl C–H bonds of *N*-methoxy α,β-unsaturated amides **33** (Scheme 17).[27a] In the reaction, CONH(OMe) played a dual role of a directing group as well as an internal oxidant for the construction of synthetically important 1,3-dienamides **34** in good yield and high *E*-stereoselectivity. The formation of a five-membered ruthenacycle




Scheme 16 Acylsilane-directed *ortho*-C($sp^2$)–H olefination.



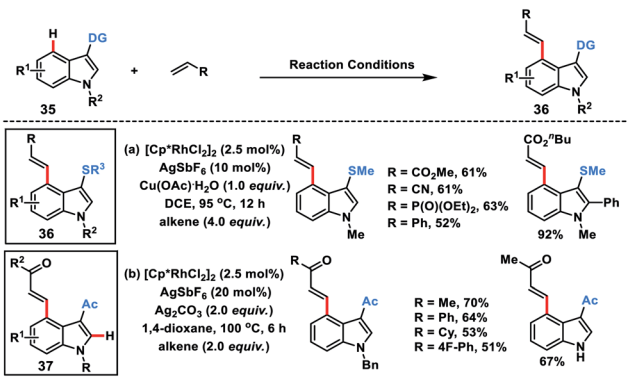

Scheme 17 Ru(II)-catalysed olefination of α,β-unsaturated amides.




Scheme 18 Proposed mechanism for Ru-catalysed olefination of α,β-unsaturated amides.

through reversible C–H activation took place followed by the alkene insertion to form a seven-membered ruthenacycle intermediate **B** (Scheme 18). β-Hydride elimination followed by reductive elimination generated a Ru(0) species which underwent N–O bond insertion to afford the Ru(II)-amide intermediate **D**. Finally, protonation with PivOH led to the formation of the desired product and Ru(II)-catalyst to continue the catalytic cycle. Later, the same group extended the olefination reaction of *N*-methoxy α,β-unsaturated amides with other transition metals such as Ir and Co. Ir-catalysed olefination reaction occurred in the presence of an inexpensive hydrogen acceptor chloranil and afforded the desired products in good yield and stereoselectivity.[27b] Similarly, construction of conjugated dienes was achieved by using [Cp*Co(CO)$I_2$]-complex as the catalyst and AgOAc oxidant.[27c]

Miura's group in 2018 disclosed a Rh-catalysed thioether directed C-4 selective olefination of indoles **35** through a five-membered metallacycle intermediate (Scheme 19a).[28a] The transformation was applicable to a wide range of electron-deficient alkenes as well as styrene derivatives and afforded C-4 olefinated products **36** in good yield with *E* selectivity. The




Scheme 19 Rh-catalysed thioether & acetyl-directed C-4 olefination of indoles.

easy transformation of the thioether directing group was an added synthetic advantage to the reaction.

Punniyamurthy and co-workers recently developed a Rh-catalysed C-4 alkenylation of indoles **35** with allylic alcohols employing weakly coordinating carbonyl as the directing group (Scheme 19b).[28b] Allyl alcohols served as either an alkenylating or alkylating agent depending on the additive used. Usage of $Ag_2CO_3$ resulted in β-hydride elimination while the presence of NaOPiv led to the alkylated products. A series of substituted indoles reacted with different allyl alcohols to afford olefinated products **37** in good yield and selectivity. Allyl alcohols in the presence of a Rh-catalyst and under basic conditions were converted into enones which served as the activated alkenes in the Rh-catalysed olefination reaction.

Indole NH directed Rh-catalysed *ortho*-di-olefination of 2-arylindoles was presented by Huang and co-workers in 2018.[29] It is worth mentioning that when the reaction was performed in DMF instead of EtOAc, formation of 6*H*-isoindolo[2,1-*a*]indole took place through intramolecular aza-Michael reaction.

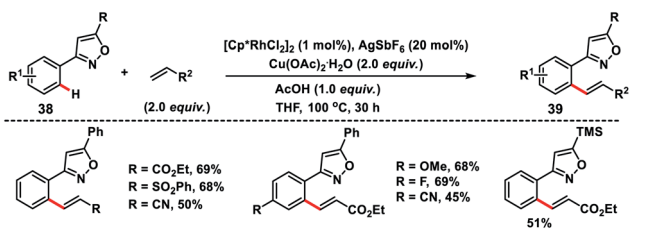
Kapur and co-workers demonstrated a precise catalyst-controlled selective C–H olefination of isoxazoles **38**. When a cationic rhodium catalyst is used, the transformation was dictated by the cationic nature of the catalyst, and the strong coordination of isoxazole nitrogen led to *ortho*-C($sp^2$)–H olefination of proximal aryl rings **39** (Scheme 20),[30] while a palladium-catalyst prefers electrophilic C–H activation due to the covalent nature of the catalyst and olefination took place at the distal position of the directing group. The reaction followed an interesting mechanism as KIE studies *via* both parallel and competitive reactions indicated the absence of the primary kinetic isotope effect highlighting that C–H activation was not the rate limiting step. The C–H activation step in the transformation most probably proceeds through a base-assisted internal electrophilic substitution (BIES) reaction and site selectivity was governed by the affinity of the Rh-catalyst for isoxazole nitrogen. Du and co-workers reported Rh(III)/[BMIM]$NTf_2$ as a reusable catalytic system for the *ortho*-olefination of arenes at room temperature.[31] The ionic liquid used in the transformation is chemically stable and non-volatile accounting for an environment friendly protocol.

### 2.2. Atroposelective C($sp^2$)–H olefination

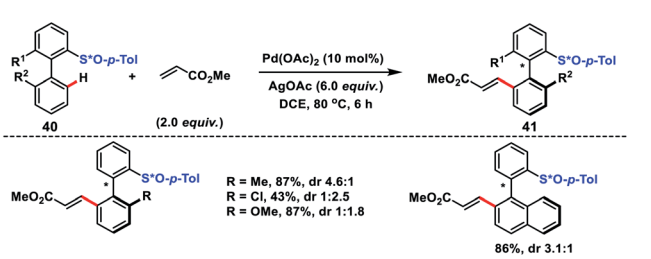
Axially chiral biaryl scaffolds are omnipresent in a class of natural products and biologically relevant compounds, and are also used as chiral ligands or catalysts in a series of asymmetric syntheses.[32] In the literature many elegant strategies are present for the synthesis of axillary chiral biaryls such as asymmetric Suzuki–Miyaura couplings, desymmetrization of prochiral biaryl compounds, atroposelective cleavage of the biaryl lactones, asymmetric oxidative homocouplings *etc.* Recently, asymmetric C–H activation has emerged as a potential alternative to access chiral biaryl compounds in a single step and atom economic way.

Synthesis of axillary chiral biaryls through directing group assisted C($sp^2$)–H olefination was first reported by Colobert and co-workers in 2013 (Scheme 21).[33] The first outcome in the synthesis of axillary chiral biaryls was reported by them. They used enantiopure *p*-tolyl sulfoxide **40** as the directing group which induced the atropodiastereoselectivity during the olefination process. In the protocol electron-deficient acrylates served as efficient coupling partners with a variety of biaryl systems and afforded corresponding products **41** in moderate to good yield. The observed atroposelectivity during the transformation probably arose from diastereomeric discrimination during the cyclometallation step. This resulted in an atropoenriched Pd–C bond formation at the sterically less hindered side, *i.e.* opposite to the bulky *p*-tolyl group. Yang and co-workers reported a similar Pd-catalysed atroposelective C–H olefination through dynamic kinetic resolution for the synthesis of axially chiral phosphine oxide-based compounds.[34] (*S*)-(−)-Menthyl phenylphosphinate served as the directing group as well as induced atropodiastereoselectivity during the olefination process.

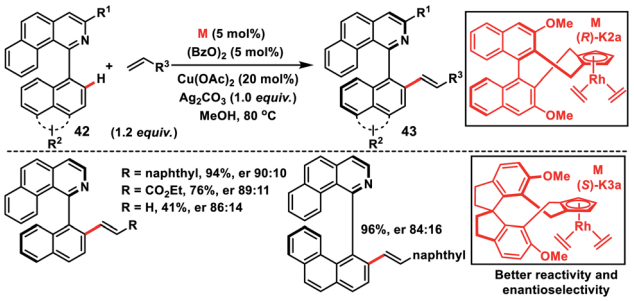
Asymmetric Rh(I)-catalysed introduction of axial chirality in biaryl systems **42** was developed by You and co-workers in 2014 (Scheme 22).[35a] The major challenge in the construction of axially chiral biaryls was the formation of cyclometallated species during C–H activation and it requires co-planarity of the two sterically hindered arenes which raised the energetic barrier of the reaction. For the first time chiral Cp rhodium complexes were used for the facile enantioselective synthesis of axially chiral biaryl systems in excellent yield and good enantioselectivity through the C–H activation process. Diversely substituted biaryls reacted well with a series of olefins like 2-vinylnaphthylene, styrenes and electron-deficient alkenes to grant the desired products **43**. The same group in 2016 came up with another modified Rh(I)-catalyst with chiral Cp 1,1′-spiroindane ligands to synthesize axially chiral biaryls (Scheme 22).[35b] The modified Rh-complex (*S*)-K3a showed better activity and the reaction occurred even at room temperature providing products with improved enantioselectivity. The chiral biaryl




Scheme 20 Rh-catalysed isoxazole-directed olefination of proximal aryl rings.




Scheme 21 Chiral auxiliary-induced atroposelective C–H olefination.

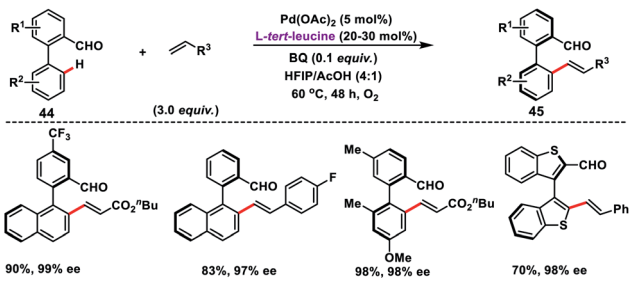



Scheme 22 Chiral Rh(I)-catalysed enantioselective C–H olefination.

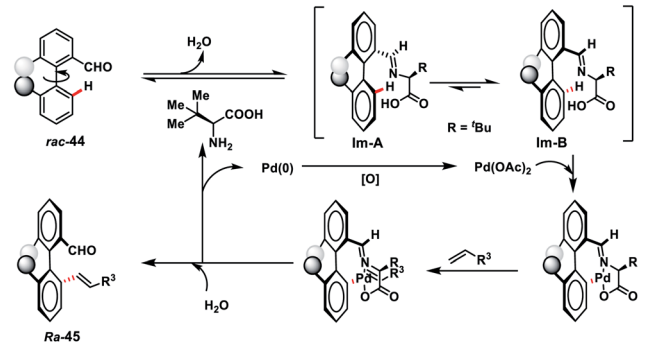
products were used as suitable ligands in Rh-catalysed reactions.

Pd-catalysed synthesis of axially chiral biaryls *via* C–H olefination reaction engaging *tert*-leucine as an inexpensive, catalytic and transient chiral auxiliary was developed by Shi and co-workers (Scheme 23).[36a] The reaction was compatible with diverse substituted biaryls **44** and several olefins including electron-deficient styrenes affording products **45** in good yield and excellent enantioselectivity. The reaction was proposed to progress *via* a reversible reaction of the chiral amino acid with **44** to form imine intermediates **IM-A** or **IM-B**. Due to the steric interaction, the C–H bond of one of the diastereomers cleaved preferentially to form an axially stereoenriched axial-biaryl palladacycle intermediate. The palladacycle intermediate underwent a typical Heck reaction followed by *in situ* hydrolysis of imine to yield chiral biaryls **45** (Scheme 24). Furthermore, the synthetic utility of the protocol was demonstrated by the asymmetric total synthesis of TAN-1085 in good yield and excellent enantioselectivity (>99% ee).[36b] The same group further elaborated an atroposelective C–H olefination reaction by the synthesis of highly enantiopure atropoisomers having pentatomic heteroaromatics (Scheme 23).[36c] The protocol was found to be well tolerated in terms of different five-membered biaryls containing benzothiophenes and benzofurans and provided axially chiral pentatomic biaryls in good enantioselectivity.

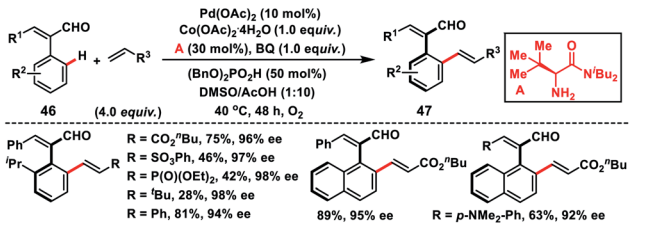
Recently, Shi's group has developed a Pd-catalysed protocol for the synthesis of challenging axially chiral styrenes **47** by introducing a bulky amino amide as the transient chiral auxiliary **A** (Scheme 25).[37] Induction of chirality was challenging in cinnamaldehydes due to their relatively lower rotation barrier.




Scheme 23 Synthesis of axially chiral biaryls using a transient chiral auxiliary.



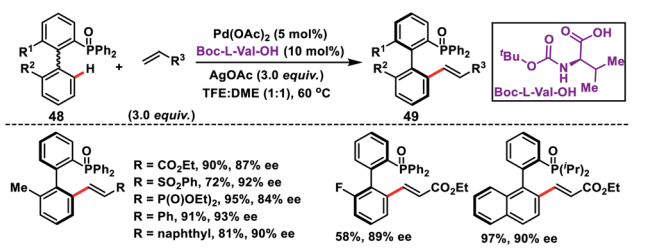

Scheme 24 Proposed path involved in the transient chiral auxiliary catalysis.



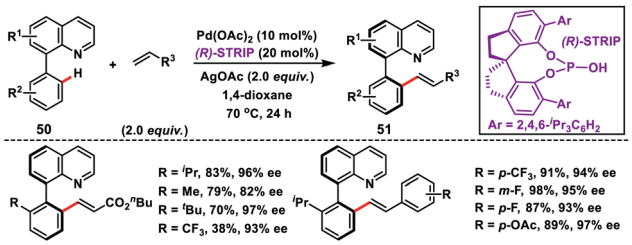

Scheme 25 Synthesis of axially chiral styrenes enabled by an amino amide transient directing group.

In particular, sterically bulky substituents *ortho* to the chiral axis were necessary to ensure the enantioselectivity. Cinnamaldehydes **46** having a relatively large substituent at the *ortho* position have a higher rotational barrier compared to the smaller group. The successfully isolated palladacycle intermediate was found to have the same stereochemistry as the product.

Pd-catalysed induction of atropoisomerism in biaryl systems by means of chiral ligands was first adopted by Yang and co-workers in 2017 to synthesize chiral atropoisomeric biaryl phosphine–olefins **49** (Scheme 26).[38] They used MPAA Boc-L-Val-OH to execute phosphene-directed C–H olefination through dynamic kinetic resolution (DKR). Phosphene oxide **48** not only served as a directing group for C–H activation, but also controlled the outcome of the products. It was interesting to note that the electronic properties of the substituent on the biaryl system have a significant impact on the product yield and enantioselectivity.




Scheme 26 Boc-L-Val-OH ligand-assisted synthesis of chiral biaryl phosphine-olefins.

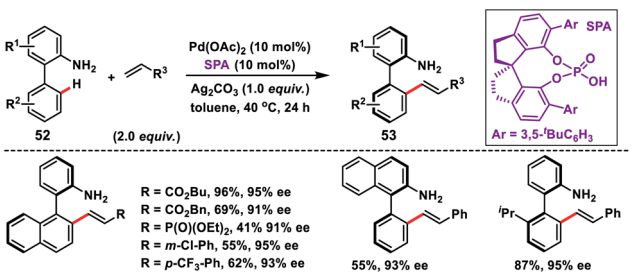



Scheme 27 (*R*)-STRIP as an efficient chiral ligand for the synthesis of axially chiral quinoline biaryls.

Shi and co-workers demonstrated chiral spiro phosphoric acid (*R*)-STRIP as an efficient chiral ligand for the Pd-catalysed synthesis of axially chiral quinoline-derived biaryls **51** in good yield and excellent enantioselectivities (99% ee) (Scheme 27).[39a] The better outcome of the enantioselectivity was due to the narrow and well-defined channel of SPAs which provided more rigid pockets than the BINOL-derived counterparts. This led to a healthier steric interaction with substrates **50**. Density functional theory (DFT) suggested that the chiral phosphate acted as the counterion to stabilize Pd, while acetate ion served as the base in the cyclometallation deprotonation type C–H activation. Recently, a modified chiral spiro phosphoric acid (SPA) ligand was developed by the same group to execute free amine-directed C–H olefination leading to chiral biaryl-2-amines **53** in excellent yield and enantioselectivity (Scheme 28).[39b] The modified ligand showed an enhanced reactivity and its loading could be reduced up to 1 mol% without any alteration of enantiocontrol in gram scale synthesis.

## 3. Distal C(sp$^2$)–H olefination

Directing group assisted *ortho*-functionalization is rather facile considering the kinetic and thermodynamic stability of five, six and seven membered metallacycle transition states. However, to activate the distal C–H bond, a relatively large and energetically unfavorable 11, 12 or even higher atom containing metallacycle intermediate needs to be formed. As a result, controlling the selectivity is a major concern. Thus, it is vital to recognize the distal and geometrical relationships between the functional group and C–H bond of the substrate to overcome the entropy demand owing to the macrophane-like transition state and to achieve selective C–H activation.

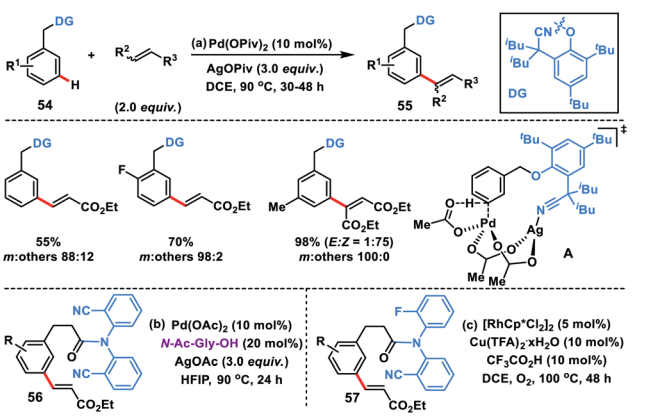



Scheme 28 Pd(II)-catalysed free-amine-directed atroposelective C–H olefination.

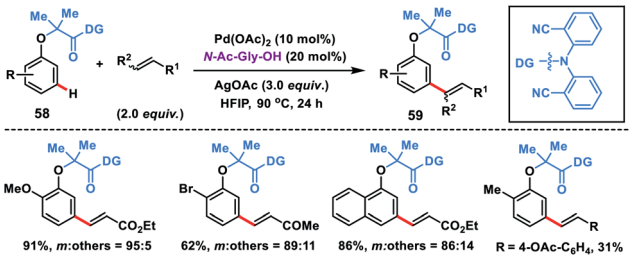
### 3.1. *meta*-C(sp$^2$)–H olefination

As an elementary step towards distal functionalization, Yu and co-workers in 2012 designed a U-shaped nitrile-based template. The template delivered the palladium metal to the vicinity of the *meta*-C–H bond of the tethered arene to execute C–H olefination with excellent selectivity overriding the electronic and steric bias (Scheme 29a).[40a] *meta*-Selective olefination (95%) of toluenes **54** was achieved in the presence of Pd(OPiv)$_2$-catalyst and AgOPiv oxidant in DCE. The strategy was also successfully applied to the *meta*-olefination of hydrocinnamic acid derivatives **56** under modified reaction conditions. The reaction medium had a significant influence on the stability of the transition state as showcased by the change in the *meta*-selectivity on changing the solvent. DFT studies for *meta*-olefination of toluenes revealed that the C–H activation proceeds through a concerted metalation–deprotonation pathway and it is also the most energy demanding path. Also, C–H activation in a nitrile-based template occurred *via* the formation of a heterodimeric Pd–Ag transition state **A** having lower energy than any other form of palladium species (Scheme 29b).[40b] Yu and co-workers developed rhodium-catalysed *meta*-C–H olefination of hydrocinnamic acid derivatives **57** by a slight modification of the template used in Pd-catalysis (Scheme 29c).[40c] The approach was much ecofriendly as oxygen served as an external oxidant in the presence of a catalytic copper salt.

The directing group strategy for *meta*-C–H olefination was extended to phenol derivatives **58** by the same research group using a nitrile-based end-on template (Scheme 30).[41a] Selective *meta*-functionalization of phenol was more challenging considering that the *meta* position of the phenol is least active towards electrophilic attack. After rigorous optimization *meta*-olefinated products **59** were obtained in good yield and selectivity in the presence of Pd(OAc)$_2$-catalyst, ligand *N*-Ac-Gly-OH and AgOAc oxidant in HFIP. Different phenol scaffolds including *ortho*-brominated substrates were well-suited under the reaction conditions and coupled with activated alkenes



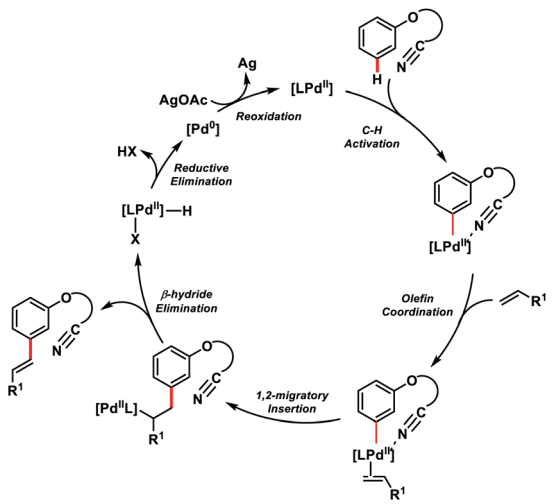

Scheme 29 *meta*-C–H olefination of toluenes and hydrocinnamic acids.



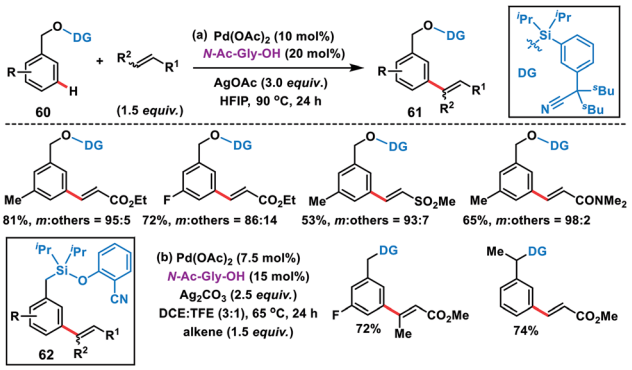

Scheme 30 Pd-catalysed *meta*-selective C–H olefination of phenols.

including electron-deficient styrenes. The mechanistic investigation[41b] indicated that the MPAA ligand *N*-Ac-Gly-OH not only acted as a dianionic bidentate ligand rather also as the internal base to abstract protons through the amidate group (Scheme 31).

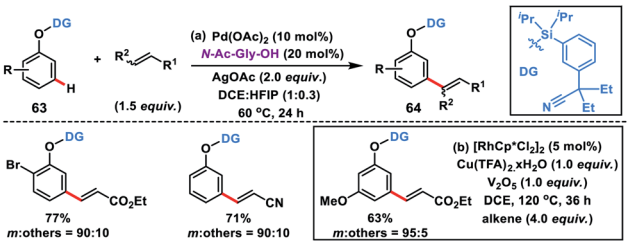
Tan's group further developed the template-based strategy for *meta*-selective C–H olefination of benzyl alcohols **60** using a silicon-tethered nitrile-based directing group (Scheme 32a).[42a] Easy incorporation of the template and its removal made the methodology more facile. *meta*-Selectivity up to 98 : 2 was achieved irrespective of the electronic nature of the substrate in the presence of a Pd(II)-catalyst, *N*-Ac-Gly-OH ligand and HFIP solvent. Extending the silyl-tethered directing group-assisted *meta*-olefination reactions, our group successfully olefinated benzylsilanes with very high selectivity (*m* : others > 20 : 1) to obtain **62** in good yields (Scheme 32b).[42b] Regioselective bis-olefination of benzylsilanes was conducted employing removable 2-hydroxy-5-methoxybenzonitrile. The silyl linker could be easily removed leading to the synthesis of olefinated toluenes, benzaldehydes and benzyl alcohols. Xu, Zhou and co-workers demonstrated *meta*-selective C–H olefination of phenols **63** using Pd and Rh catalysts simultaneously *via* incorporating a traceless organosilicon template bearing nitrile as the directing group (Scheme 33). The Pd-catalysed reaction proceeded well with AgOAc oxidant (Scheme 33a),[42c] while the




Scheme 31 Catalytic cycle of *meta*-C–H olefination.



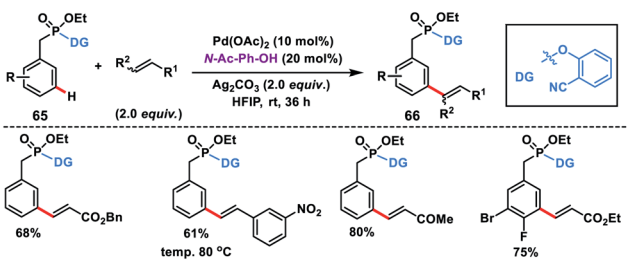

Scheme 32 Si-tethered nitrile-based directing group assisted *meta*-selective olefination of benzyl alcohol and toluene derivatives.



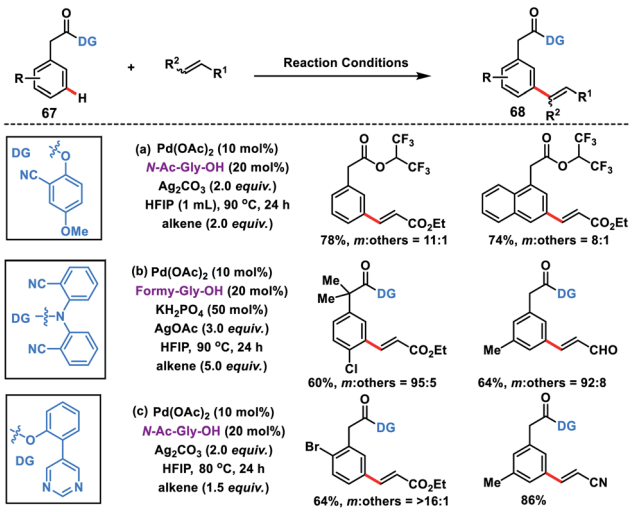

Scheme 33 *meta*-Olefination of phenols using an organosilicon template.

MPAA ligand *N*-Ac-Gly-OH, hydrated copper salt oxidant and $V_2O_5$ co-oxidant are vital for the Rh-catalysed *meta*-olefination of phenols (Scheme 33b).[42d] The protocols were viable for a large range of olefins along with diversely substituted phenols and afforded the desired *meta* products **64** in good yield and excellent selectivity. *meta*-Olefinated phenols could be further utilized for coumarin synthesis after removal of the directing group.

*meta*-C–H olefination of benzyl phosphonates **65** at room temperature was first reported by our group facilitated by a novel phosphonate-based template tethered with a 2-hydroxybenzonitrile directing group (Scheme 34).[43] The reaction was performed in the presence of Pd-catalyst, *N*-Ac-Ph-OH ligand and silver oxidant in HFIP at room temperature to give products **66** in excellent yield and selectivity. Notably, di-olefination occurred at an elevated temperature (80 °C).




Scheme 34 *meta*-Olefination of benzylic phosphonate esters.



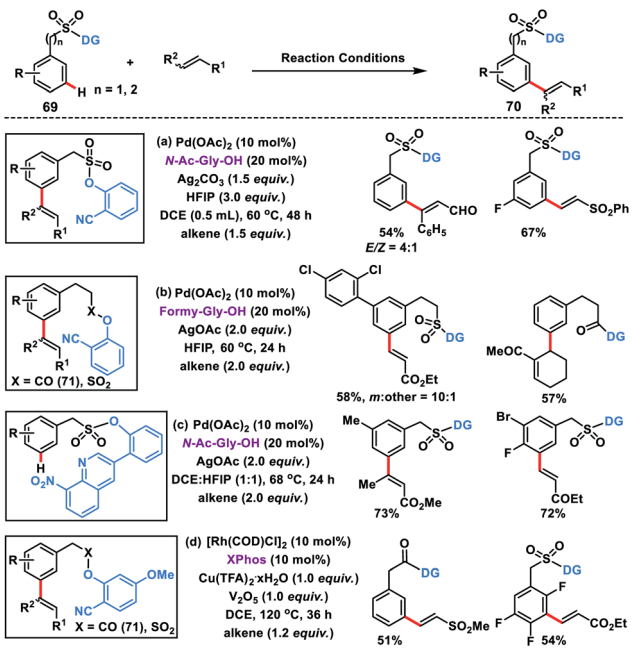

Scheme 35 *meta*-Selective C–H olefination of phenylacetic acids.

Considering the importance of arylacetic acids **67** in the pharmaceutical industry, our group developed the first *meta*-selective olefination of such molecules with the assistance of the 2-hydroxy-5-methoxybenzonitrile auxiliary. The reaction proceeded well in a combination of Pd-catalyst, MPAA ligand *N*-Ac-Gly-OH and a suitable silver oxidant, and afforded products **68** in good yield and selectivity (Scheme 35a).[44a] However, HFIP solvent used in the reaction led to *trans*-esterification thereby removal of the directing group, hence affecting the overall yield. Later on, Yu and co-workers reported *meta*-olefination of phenylacetic acids in the presence of modified MPAA ligand formyl-Gly-OH (Scheme 35b).[44b] Yu group reported a strongly coordinating pyrimidine-based template[44c] to execute *meta*-C–H olefination of arylacetic acids in order to broaden the substrate scope (Scheme 35c).

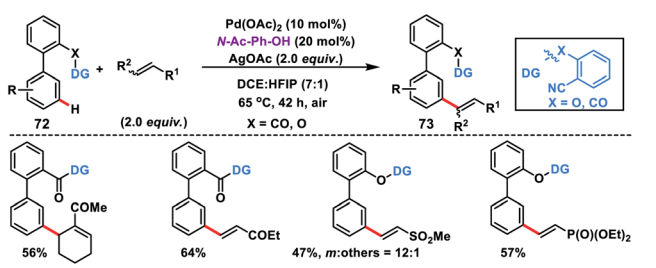
Our group developed Pd(II)-catalysed *meta*-C–H olefination of benzylsulfonyl ester derivatives **69** in the presence of *N*-Ac-Gly-OH ligand and $Ag_2CO_3$ oxidant to yield the desired products **70** in good yield and selectivity (Scheme 36a).[45a] Homo-diolefination and sequential hetero-diolefination in one pot with exclusive *meta*-selectivity and high yield were observed. Capitalizing on the same template our group extended the scope of *meta*-olefination for arylethane acid derivatives using sulfonyl **69** and carbonyl **71** linker (Scheme 36b).[45b]

Being a weak coordinating group nitrile can be easily displaced in the presence of a strong coordinating group leading to deactivation of the catalyst. To overcome such a limitation, our group reported a strongly coordinating 8-nitroquinoline-based template tethered by a sulfonyl group for the selective *meta*-olefination (Scheme 36c).[45c] The strongly coordinating 8-nitroquinoline not only directs the metal towards the *meta*-position but also stabilizes the palladacycle through its high coordinating ability. Later, the scope of the *meta*-olefination of benzylsulfonyl esters **69** and phenylacetic acid derivatives **71** was extended by our group through Rh-catalysis in the presence of XPhos ligand (Scheme 36d).[45d] Unlike Pd(II), the use of Rh(I) limits the transesterification while DCE was found to be a more suitable solvent than HFIP. UV studies suggest that Rh(I) species *in situ* transformed into its active form Rh(III) intermediate and catalysed the reaction.

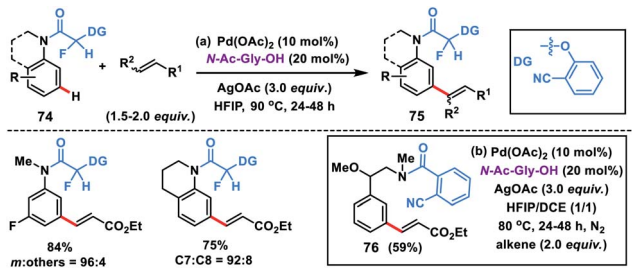
Our group in 2016 explored the distal C–H olefination of biphenyl carboxylic acids and phenols **72** with the help of a carbonyl linker and nitrile as the weak coordination group. The reaction proceeded well in the presence of a Pd-catalyst along with the MPAA ligand *N*-Ac-Ph-OH and AgOAc oxidant to deliver highly selective *meta*-olefinated products **73** (Scheme 37).[46a] Both substrates showed almost similar reactivity under the optimized conditions, which validated the principle of the selectivity–reactivity paradigm. Recently, Yu group developed a 2-pyridone ligand-promoted *meta*-selective C–H olefination of biphenyl nitrile derivatives under Pd-catalysis.[46b] *meta*-Selective olefination in the reaction was completely controlled by the ligand without the direct involvement of the directing group. The computational study suggested that a Pd–Ag bimetallic bridge forms with the involvement of 2-pyridone and acetate molecule to lower the energy barrier, and C–H activation proceeded through a cyclometallation–deprotonation pathway.



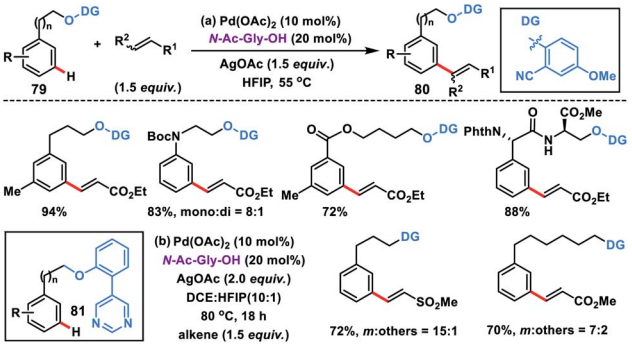

Scheme 36 Directed *meta*-olefination of alkylbenzene derivatives.




Scheme 37 *meta*-C–H-olefination of biphenyl carboxylic acids and phenols.




Scheme 38 *meta*-Selective C–H olefination of amines and heteroaromatics.




Scheme 40 *meta*-C–H olefination of arenes across different linker lengths.

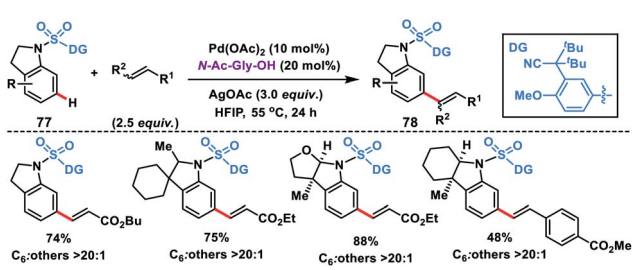
The use of a carbonyl-based template with an α-fluoro substituted nitrile auxiliary for the *meta*-olefination of anilines and N-heteroaromatic compounds **74** was expanded by Yu and co-workers (Scheme 38a).[47a] The presence of a fluorine atom α to the carbonyl group led to a conformational change and the carbonyl group drifted away from the *ortho*-C–H bond. The same α-fluoro substituted nitrile auxiliary was also applicable to aniline derivatives for *meta*-C–H olefination **75** with diverse activated alkenes. Li and co-workers in 2015 demonstrated *meta*-selective olefination of phenylethylamines **76** by using 2-cyanobenzoyl as the directing auxiliary (Scheme 38b).[47b] The same group later developed a carbamate-linked directing group by incorporating $CO_2$ into a nitrile-based template for the Pd-catalyzed *meta*-olefination of anilines.[47c]

Electrophilic attack on indoline moieties is more favourable at the *ortho* and *para* positions, therefore *meta*-functionalizations of these substrates are extremely challenging. Yu and co-workers reported *meta*-selective olefination of indolines **77** by incorporating an electron-withdrawing sulfonyl bridge with an appropriate nitrile auxiliary (Scheme 39).[47d] The MPAA *N*-Ac-Gly-OH ligand-assisted *meta*-olefination yielding **78** proceeded through a metalation deprotonation path and provided a selectivity of >20 : 1 with good yields. Also, a series of N-heterocycles were olefinated at the distal position using the sulfonyl bridged template with a modified auxiliary.[47e]

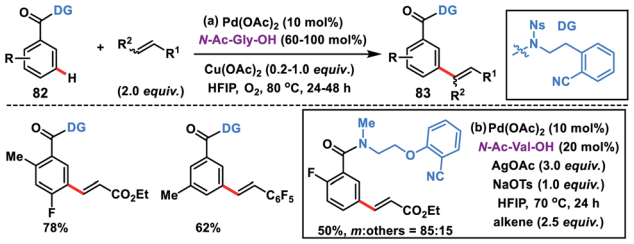
*meta*-Olefination of long chain arenes and tethered alcohols with very high regioselectivity was discovered by Xu, Jin and co-workers using a 2-cyanophenol based template (Scheme 40a).[48a] The olefination reaction proceeded well in the presence of a Pd-catalyst, MPAA ligand *N*-Ac-Gly-OH and a silver salt as the oxidant. A series of substrates such as 3-phenylpropanols, 2-phenoxyethanols, and 2-(phenylamino)ethanols including dipeptide-derived substrates **79** were effectively olefinated affording **80** in high yields and selectivity. In 2018, our group developed a strongly coordinating pyrimidine-based directing template for *meta*-functionalization of the substrate **81** which differed widely in the linker chain length (up to 20 atoms) (Scheme 40b).[48b] Different alkenes and arenes were tolerated under the optimized reaction conditions.

*meta*-Olefination of relatively electron-poor benzoic acid derivatives **82** was challenging and first reported by Li and co-workers in 2016 using an *N*-nosyl-substituted amide bridged template (Scheme 41a).[49a] A range of benzoic acid derivatives underwent *meta*-olefination to produce **83** in good yields and selectivity. Use of molecular oxygen as a terminal oxidant in the presence of a catalytic copper salt made the protocol more convincing. Later, Yu group designed a conformationally more flexible 2-(2-(methylamino)ethoxy)benzonitrile-based template for the *meta*-olefination of benzoic acids (Scheme 41b).[49b] They used an *N*-methylated amide having an additional ether linkage for the elongation of the directing group and performed the reaction with *N*-Ac-Val-OH as a ligand and AgOAc oxidant along with an NaOTs additive. Mechanistic investigation revealed that the reaction proceeded through a bimetallic Ag–Pd heterodimer intermediate. KIE studies suggested that the C–H activation step was the rate-limiting step.

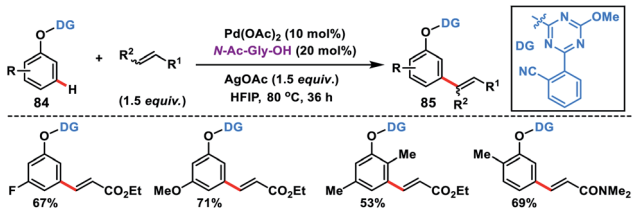
In 2019, Yu and co-workers synthesized a bifunctional template to accomplish Pd-catalysed *meta*-olefination of phenols **84** in the presence of *N*-Ac-Gly-OH ligand (Scheme 42).[50] The synthesized olefinated product **85** underwent Ni-catalysed ipso coupling of the C–O bond of the phenols with aryl




Scheme 39 *meta*-Selective olefination of indoline derivatives.




Scheme 41 Directing group-assisted *meta*-C–H olefination of benzoic acids.

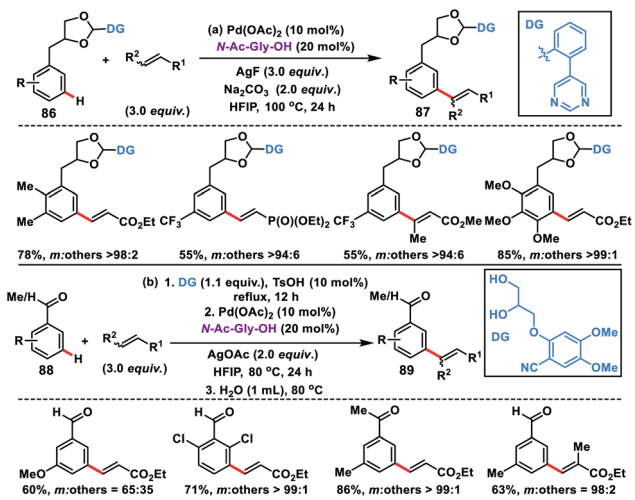



Scheme 42 Triazine linked template-assisted *meta*-olefination of phenols.

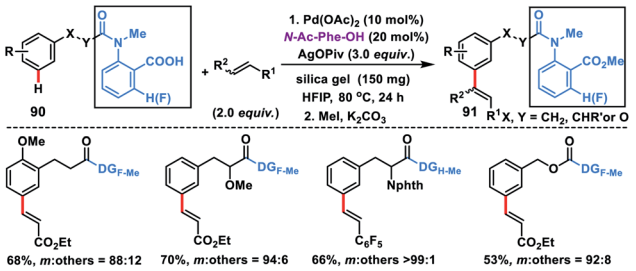
boronic acid to yield 1,3-disubstituted arenes. Both steps of the reaction could be performed in one pot.

Use of an acetal or a ketal linker for the *meta*-olefination of 1,2-diols **86** and aldehydes or ketones **88** was developed independently by Kong and Ji group in 2019. Kong and co-workers disclosed the Pd-catalysed *meta*-olefination of 3-phenylpropane-1,2-diol **86** using the strongly coordinating pyrimidine directing group to yield **87** (Scheme 43a).[51a] The directing template cleaved up to some extent during the reaction resulting in the mixture of products. Later, Xu, Jin and co-workers used a combination of a Pd-catalyst and *N*-Ac-Gly-OH ligand for the *meta*-olefination of electron-poor aromatic aldehydes and ketones **88** using an acetal and ketal linker (Scheme 43b).[51b] The reaction was performed in one pot with sequential protection of carbonyl by a 1,2-diol-based nitrile template and Pd-catalysed C–H olefination reaction to yield **89** followed by removal of the template by a simple hydrolysis to access *meta*-olefinated aldehydes or ketones.

In 2019, Li and co-workers first discovered the carboxylic acid group as the directing auxiliary for *meta*-olefination (Scheme 44).[52] The reaction proceeded through the assistance of the carboxylic acid group, which binds with Pd possibly through $k^2$-coordination mode instead of $k^1$ thus overriding *ortho*-C–H activation. The reaction proceeded well with a series a substituted arenes **90** and different olefins including styrenes and delivered *meta*-olefinated products **91** in good yield and




Scheme 43 Acetal or ketal linker-assisted *meta*-C–H olefination of arene-tethered diols and aldehydes or ketones.

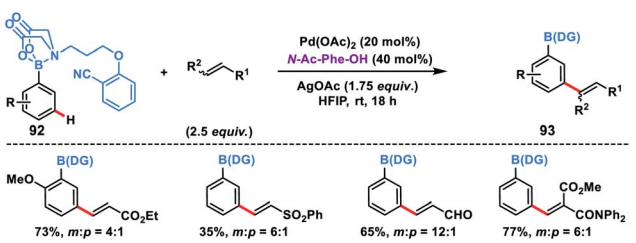



Scheme 44 Carboxy group directed *meta*-C–H olefination of alkylbenzenes.

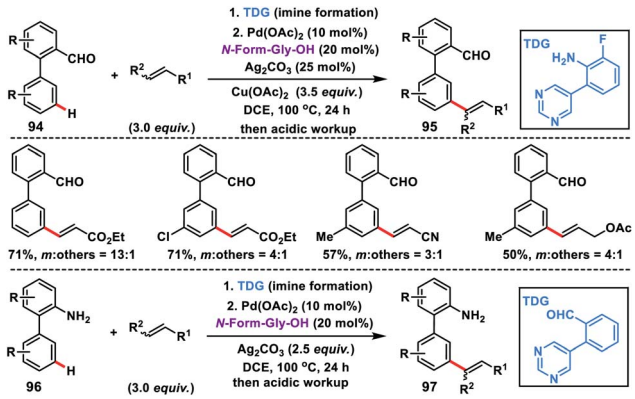
selectivity. To verify that the Pd coordinates in $k^1$ mode in the *ortho*-C–H activation, a directing group without the fluorine substituent at the *ortho*-position was employed which afforded good remote selectivity hence supporting the hypothesis. The remote selectivity in this reaction could be rationalized as that perhaps both proximal and *meta*-cyclopalladation isomers were formed but the *meta* one was more susceptible towards functionalization due to its weaker coordination.

Recently, Spivey, Cordier and co-workers presented a novel *N*-methyl iminodiacetic acid (MIDA) boronate derivative as the protecting cum directing group for the Pd-catalysed *meta*-selective olefination of boronic acids **92** (Scheme 45).[53] MIDA-DG boronate could be easily accessed through condensation with boronic acid and also can be removed under mild basic conditions. The reaction tolerated a series of substituted phenylboronic acids and activated olefins to give *meta*-olefinated products **93** in moderate yield and selectivity. The catalytic efficiency, selectivity and reaction range of this protocol needed to be further improved as it provided path for several inaccessible boronic acid derivatives.

In recent times use of transient directing groups has emerged as a powerful and attractive strategy in chemical transformations as an alternative to covalently linked directing auxiliaries. The first study on transient directing *meta*-C–H olefination has been recently reported by our group, where an imine served as the linker (Scheme 46).[54] We developed a modified pyrimidine-based template linked through an imine which served as the directing template for *meta*-olefination of synthetically important biphenyl aldehydes **94** and amines **96**. In the case of biphenyl aldehyde, copper salt served as the oxidant in the presence of a catalytic silver salt while in biphenyl amine the silver salt was the sole oxidant. The MPAA ligand *N*-




Scheme 45 *meta*-Olefination of aryl boronic acids directed by MIDA-derived boronate ester.



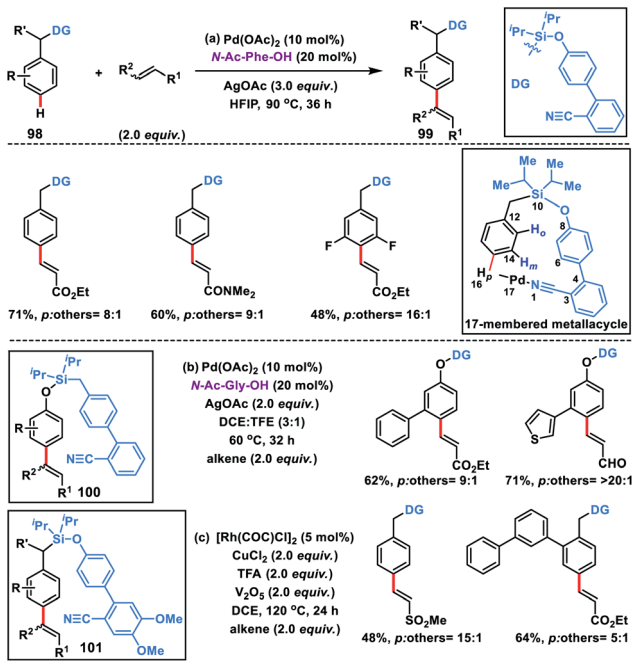

Scheme 46 Imine as a transient-directing group for *meta*-C–H olefination.

formyl-Gly-OH was essential for the reaction and the imine linkage hydrolysed *in situ* during acidic workup.

### 3.2. *para*-C($sp^2$)–H olefination

Electrophilic substitution reactions in benzene at *ortho* and *para* positions are governed by the electronic nature of the substituents present. However, regioselective functionalizations at the *para*-position are scarce and only a few reports are available in the literature which are governed by the steric and electronic nature of the substituent. Till 2015, no reports were available which could address the issue on a striking scale for highly selective *para* functionalization of arenes.

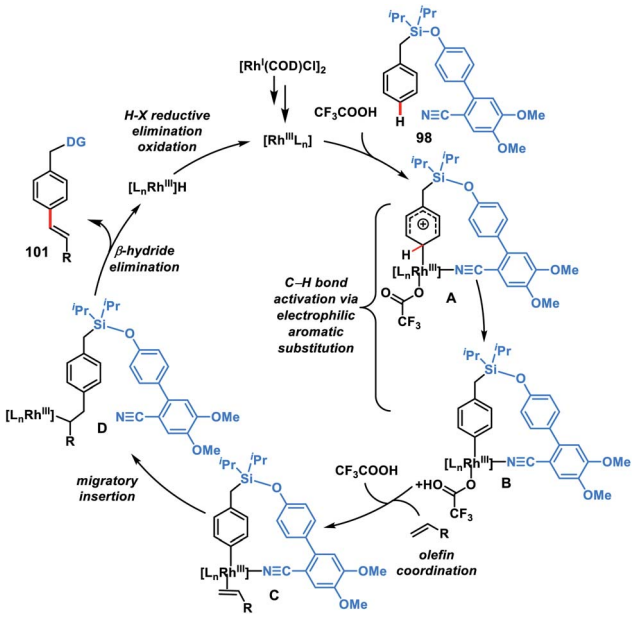
For the first time a concrete solution to address the *para*-selectivity was reported by our group by extending the application of template-based directing groups (Scheme 47a).[55a] The major apprehension in *para*-C–H functionalization is to deliver the metal-catalyst towards the targeted C–H bond due its distal location in the arene molecules. Also, a weakly coordinating directing group is required for the site selective interaction of metal catalysts. Additionally, the entire catalytic cycle has to proceed through a large macrocyclic cyclophane-like (16–17 membered) transition state. To overcome these obstacles, a judicially engineered directing group, linker and its length are required to reach the target C–H bond. As an initial approach to satisfy all these requirements, a biphenyl template containing the weakly coordinating cyano group was chosen. The heteroatom of the cyano group easily coordinates with the metal-catalyst, while the biphenyl system regulates the chain length of the macrocyclic assembly. After a series of optimizations, we came up with a weakly coordinating nitrile-based biphenyl template attached to the toluene ring through a silyl linker. The substituent present on the silicon atom plays a prominent role as it exerts the Thorpe–Ingold effect and pushes the directing group towards the target position. With this directing template, a series of toluene derivatives **98** were successfully olefinated regioselectively at the *para* position in the presence of a Pd-catalyst, *N*-Ac-Phe-OH ligand and silver oxidant in HFIP solvent (Scheme 47). A diverse array of toluene derivatives coupled with several activated olefins affording *para*-olefinated products **99** in decent yield and good selectivity by overriding all sorts of electronic and steric bias present in the substrate. A series of α,β-unsaturated esters, sulfones, amides and acrylates of vitamin E and cholesterol were used as olefin coupling partners with appreciable *para*-selectivity. The directing auxiliary could be easily removed by simply treating with TBAF to yield the *para*-olefinated toluene derivatives.




Scheme 47 *para*-Olefination of toluenes and phenols using a biphenyl director.

After the successful olefination of toluene derivatives, our group extended the application of this directing template for the *para*-olefination of phenol derivatives **100** by simply swapping the oxygen and methylene group on both sides of the silyl linker (Scheme 47b).[55b] The reaction proceeded under almost similar conditions, however the ligand *N*-Ac-Gly-OH was found to be optimum in the solvent combination of DCE and TFE (3 : 1). The methodology was applicable for a wide range of phenol derivatives and activated olefins and afforded olefinated products in 81% yield with high regioselectivity (*para*/others, 10 : 1). A wide range of functional groups like amide, ester, ketone, aldehyde and sulfonyl were well tolerated under the optimized reaction conditions. Post-synthetic application of the synthesized products was illustrated by constructing valuable natural product derivatives such as ferulic acid, the anti-inflammatory artepillin C, antimicrobial plicatin B and drupanin in good yield.

In 2019, our group modified the existing biphenyl template by introducing two OMe groups in the ring having a weakly coordinating nitrile group. This modified template has a higher electron density on the directing phenyl ring and is called the second-generation template. The second-generation template with higher electron density provided a new avenue in Rh-catalysed distal C–H functionalization. Our group utilized this second-generation template for the Rh-catalysed *para*-C–H-



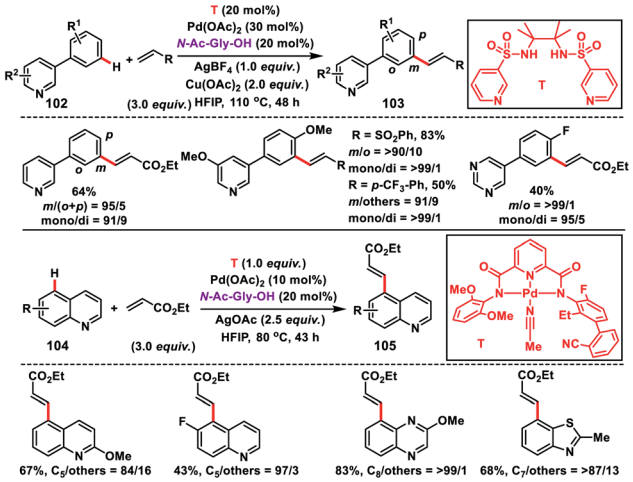

Scheme 48 Possible catalytic cycle for *para* C–H olefination.

olefination of toluenes **101** under ligand and metal oxidant free conditions (Scheme 47c).[55c] A variety of olefins were well tolerated with different toluene derivatives along with the α-substituted one. Intermolecular isotope labelling experiments were performed and a $P_H/P_D$ value of 2.9 and $k_H/k_D$ value of 2.6 indicate that C–H bond activation is likely to be the rate-limiting step. Kinetics experiments performed showed that the reaction was first order with respect to the toluene substrate and zero order with respect to the olefin. Furthermore, DFT calculations suggested that C–H activation follows an electrophilic aromatic substitution path rather than a concerted metalation–deprotonation pathway (Scheme 48) and coordination of the nitrile with Rh stabilizes the C–H activation transition state. Computational studies suggested that the incorporation of two methoxy groups on the directing template activates the substrate towards C–H bond cleavage by lowering the energy barrier.

### 3.3. Bifunctional-directed distal C($sp^2$)–H olefination

The directing group plays an important role in the site selective activation of single C–H bonds. However, the use of these directing groups is limited due to the C–H bond distance and also due to the shape of the substrates. Also, incorporation of covalently attached directing templates in molecules lacking appropriate functional groups is not feasible. Therefore, to come up with an approach not relying on covalent interaction to reach the distal position is the need of the hour since many medicinally important heterocycles lack functional groups to tether templates covalently.

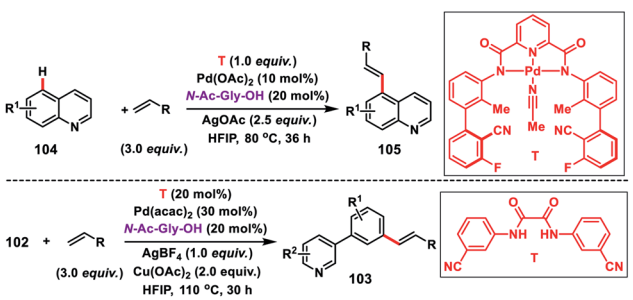
In this regard, Yu and co-workers in 2017 formulated a bifunctional template capable of coordinating with two metal centres to play two distinct roles simultaneously. For that purpose they synthesized a bis-amide based backbone-template where the sidearm holds the directing group. The bis-amide



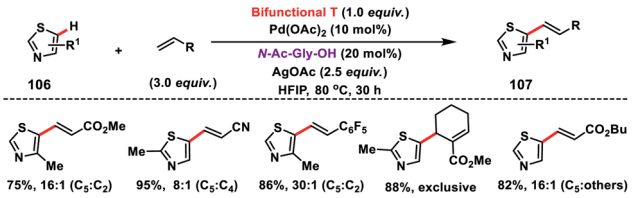

Scheme 49 Bifunctional template assisted site-selective C–H olefination.

chelate with a metal centre is responsible for substrate binding and the sidearm directing group directs the Pd-catalyst towards the specific remote C–H bond. After extensive screening they found that a sulfonamide-based template (T) derived from the sterically hindered 2,3-dimethyl-2,3-butanediamine was the most effective and afforded the olefinated heterocycles 3-phenyl pyridine **103** in decent yield and selectivity (Scheme 49).[56] The result obtained from the screening portrays the importance of conformational constraints of the backbone for remote C–H activation. In order to diversify the bimetallic catalysis, other heterocycles like quinolines **104** were chosen for the site-selective olefination reaction. However, the sulfonamide-based template was found to be unproductive, which demanded further optimization of templates. After screening of several covalent templates, they found a nitrile-based template (T) anchoring the first metal through tridentate coordination for the effective olefination of quinolines to give the product **105** in good yield and selectivity (Scheme 49).[56] However, a quantitative amount of template is required in the presence of palladium acetate-catalyst and MPAA ligand *N*-Ac-Gly-OH.

Shortly after, a similar remote C–H olefination of small heterocycles using a modified bifunctional template (T) was reported by our group (Scheme 50).[57] We synthesized a symmetrical covalently attached nitrile-based tridentate




Scheme 50 C–H olefination of heterocycles with bi- and tridentate templates.




Scheme 51 C-5 selective olefination of thiazoles with a bifunctional template.

template for the site-selective remote C–H olefination of heterocycles **104** in improved yield and selectivity. A variety of substituted quinolines and other heterocycles such as benzoxazole and benzothiazole were employed under the reaction conditions to afford products **105** in good yield and selectivity. We further designed a nitrile-based bifunctional amide derived from oxalic acid for the effective *meta*-olefination of 3-phenylpyridine derivatives **102** in synthetically useful yield and selectivity. Later, in 2019 our group utilized the same bifunctional tridentate template (T), suitable for quinoline, for the C5 selective olefination of thiazole derivatives **106** in excellent yield and selectivity (Scheme 51).[58] Admirable selectivity was observed for mono-substituted or even unsubstituted thiazoles. Diverse acrylates and electron-deficient styrenes were well tolerated and provided the desired products **107** in good yield and selectivity.

## 4. Non-directed C(sp$^2$)–H olefination

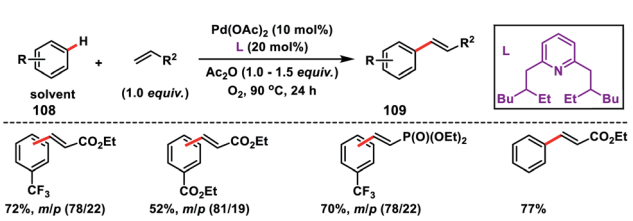
Oxidative olefination of arenes was discovered by Fujiwara–Moritani n 1967 using a stoichiometric amount of $Pd(OAc)_2$ and excess arenes. The major concerns in the non-directed approach are controlling the regioselectivity, use of excess arenes and harsh reaction conditions. Recently, ligand-enabled non-directed arene C–H olefination has become one of the focused areas *via* oxidative C–H activation to overcome the limitation of Fujiwara–Moritani reaction. The reaction mechanism involved in general in the non-directed C–H activation is the formation of a carbon–metal bond *via* concerted metalation–deprotonation (CMD) where a basic ligand is involved in the proton abstraction.

Yu and co-workers in 2009 reported the catalytic olefination of electron-deficient arenes **108** in good yield using the sterically demanding ligand 2,6-bis(2-ethylhexyl)pyridine which coordinates with palladium in a 1 : 1 ratio (Scheme 52).[59a] Oxygen was used as an oxidant to re-oxidize Pd(0) to Pd(II) with the help of the ligand. However, use of excess arenes (usually 20–30 equiv.) exerts a serious drawback especially for substituted arenes. A series of arenes with an electron-deficient group were olefinated with activated alkenes preferably at the *meta* position to yield **109** in good selectivity even when the substrate had an *ortho* directing functional group. A detailed theoretical study by Zhang on the Pd-catalysed olefination of electron-poor arenes concluded that the reaction follows a concerted metalation/deprotonation (CMD) step.[59b] The reaction proceeded through a six-membered metallacycle transition state and the selective *meta*-functionalization in the *ortho*-directing substrates can be rationalized by the steric repulsion caused by the ancillary pyridine type ligand as the major as well as the electronic effect.

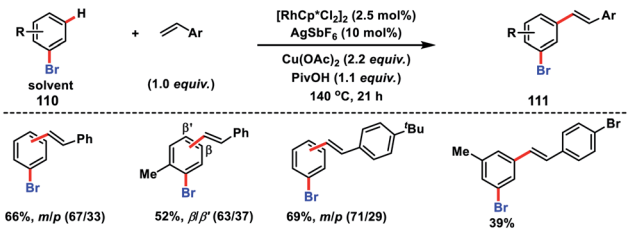
A Rh-catalysed olefination of bromoarenes **110** with substituted styrenes was demonstrated by Glorius and co-workers to synthesize *meta* and *para* products **111** (Scheme 53).[60a] It was demonstrated that bromoarenes were an integral part of the reaction serving as the terminal oxidant as well as a catalyst modifier. In 2012, Sanford's group established a facile oxidative olefination of arenes with a combination of a pyridine-based ligand 3,5-dichloropyridine and $Pd(OAc)_2$ in a 1 : 1 ratio.[60b] This reaction was more efficient in terms of yield and broader substrate scope and applicable to both electron rich and deficient arenes.

In order to address the shortcomings of previous reports Yu and co-workers demonstrated an arene limited (reagent quantity) Fujiwara–Moritani oxidative olefination. They used a bimetallic Rh(III)-complex as the catalyst and phosphene as the ligand.[61a] The bimetallic Rh(III)-complex in combination with a copper salt and $V_2O_5$ was used for the mono-olefination of electron-rich and neutral arenes in good yield. A 1 : 1 ratio of *meta*/*para* products were obtained for monosubstituted arenes and β-selective olefination for 1,2-disubstituted arenes albeit under harsh reaction conditions (140 °C). Duan and co-workers in 2014 demonstrated a Pd-catalysed oxidative olefination of arenes using the bidentate monoanionic nitrogen ligand 2-OH-1,10-phenanthroline and catalytic $Cu(OAc)_2$ along with oxygen as the external oxidant.[61b] The coordination of Pd-catalyst with the bidentate monoanionic ligand enabled the C–H activation reaction.

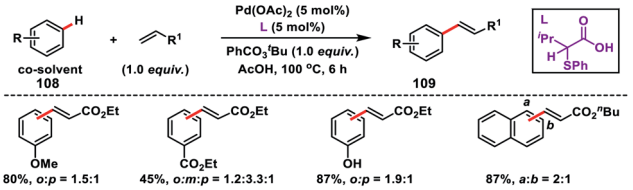
Fernández-Ibáñez and co-workers in 2017 synthesized a new class of amino acid based bidentate *S*,*O*-ligands for Pd-catalysed olefination of arenes **108** with better activity and selectivity than the Pd/pyridine combinations (Scheme 54).[62a] The late stage




Scheme 52 Pd-catalysed olefination of arenes using 2,6-dialkylpyridine ligand.




Scheme 53 Rh-catalysed olefination of bromoarenes with styrene derivatives.




Scheme 54 *S,O*-Ligand-promoted Pd-catalysed olefination of arenes.

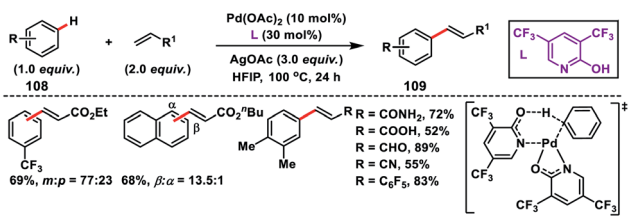
functionalization of complex molecules such as *O*-methylestrone and naproxen derivative was also successfully applied. An *S,O*-ligand was successfully utilized for the *para*-selective olefination of anilines under mild conditions and with high efficiency by the same group.[62b] The observed selectivity was solely due to the *S,O*-ligand.

Yu and co-workers in 2017 demonstrated arenes as the limiting reagent in Pd-catalysed olefination of a diverse array of electron-rich and electron-poor arenes **108** including heteroarenes and biomolecules (Scheme 55).[63] The electron deficient 2-pyridone ligand was used which acted as the X-type of ligand for palladium and also served as an internal base assisting the cleavage of C–H bonds *via* the CMD mechanism. The regioselectivity was dictated by both electronic and steric properties of the arene. Predominantly, *meta* and *para* derivatives are observed in most of the monosubstituted arenes.

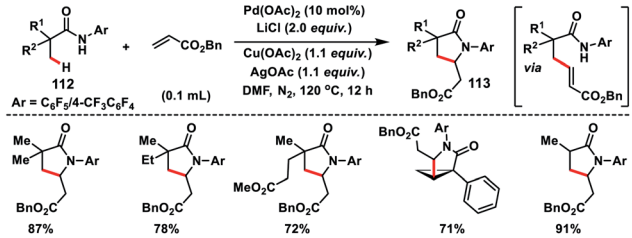
In 2018, van Gemmeren and co-workers reported Pd-catalysed arene limiting C–H olefination using two complementary ligands.[64] They used *N*-Ac-Gly-OH in combination with a 6-methylpyridine derivative both of which combine in a 1 : 1 fashion with each equivalent of the Pd-catalyst and performed the olefination of a wide range of arenes with different olefins. In the dual ligand assisted olefination *N*-acetyl amino acid served as the internal base and also assisted in the CMD step. In 2020, Zhu and co-workers reported dual ligand enabled non-directed Pd-catalysed olefination of aryl ethers with activated alkenes as well as styrenes in good yields and moderate selectivity.[65] They used a combination of *N*-acetyl leucine and an *S,O*-ligand 3-methyl-2-$^{i}$propyl-2-(phenylthio)acetic acid for better efficiency.

## 5. Directed C(sp$^3$)–H olefination

The C(sp$^3$)–H bond shows the lowest reactivity and highest thermodynamic stability, which makes its functionalization




Scheme 55 2-Pyridone ligand-enabled Pd-catalysed olefination of arenes.



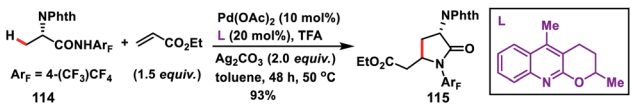

Scheme 56 Amide-directed Pd-catalysed olefination of β-C(sp$^3$)–H bonds.

more difficult yet attractive. In the past few decades, we witnessed an incredible development in C(sp$^3$)–H bond functionalization using a directing group strategy as a powerful tool to tackle stereo-, regio- and chemoselectivity. In this section, we shall be discussing directing group assisted transition-metal catalysed distal C(sp$^3$)–H bond olefination reactions.

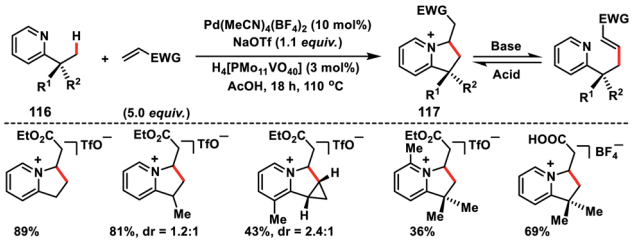
### 5.1. β-C(sp$^3$)–H olefination

Yu and co-workers in 2010 successfully achieved β-C(sp$^3$)–H olefination of amides **112** using a Pd-catalyst and subsequent aza-Michael addition to give the corresponding γ-lactams **113** (Scheme 56).[66] Along with $Pd(OAc)_2$, use of LiCl as an additive and combination of $Cu(OAc)_2$ and AgOAc in 1 : 1 ratio as the oxidant in DMF afforded high yields. The reaction was also applied to effect olefination of cyclopropyl methylene C–H bond as well as substrates containing an α-hydrogen atom. Only cyclopropyl C–H bond was selectively olefinated in the presence of an α-methyl group. A related mechanism has been suggested where the initial amide directed C(sp$^3$)–H insertion by Pd(II) leads to a five membered alkyl-palladium intermediate which underwent carbopalladation with olefin. Similarly, Yu and co-workers in 2014 carried out a β-C(sp$^3$)–H olefination of protected amino acid alanine **114** with the help of a Pd-catalyst and quinoline derived ligand. The olefinated intermediate underwent intramolecular cyclisation to afford **115** (Scheme 57).[67] The reaction delivered an excellent level of diastereoselectivity with respect to the α-centre. The reaction proceeded with an excellent level of diastereoselectivity with respect to the starting configuration at the α-centre. With the utilization of literature reports the lactam formed could be transformed into a β-olefinated α-amino acid with excellent enantiomeric excess (95%).

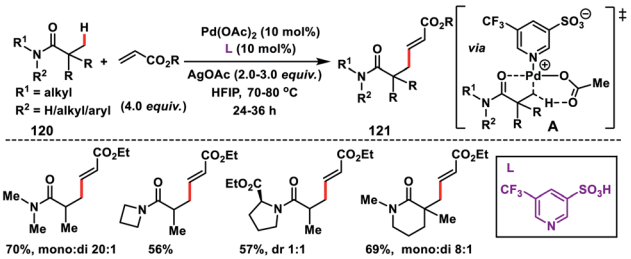
In 2011, Sanford and co-workers described a Pd-catalysed pyridine directed olefination of unactivated C(sp$^3$)–H bonds (**116**) which shaped a convenient route to a 6,5-*N*-fused bicyclic core **117** (Scheme 58).[68] After screening of several reaction conditions they found that the use of 10 mol% NaOAc, 10 mol% $Pd(MeCN)_4(BF_4)_2$ and 3 mol% $H_4[PMo_{11}VO_{40}]$ in AcOH in air




Scheme 57 Pd-catalysed C(sp$^3$)–H olefination of the amino acid alanine.




Scheme 58 Pd-catalysed olefination of β-C(sp$^3$)–H bonds.



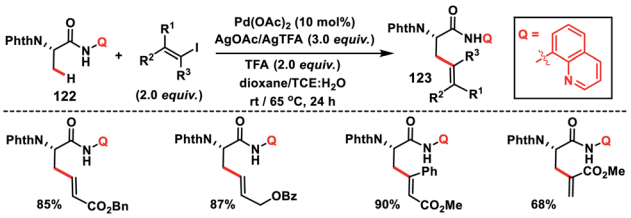

Scheme 60 Carbonyl coordination of native amides in β-C(sp$^3$)–H olefination.

was optimal. The substrate with two types of C–H bonds, *i.e.* 1° and 2°, underwent C–C coupling with >20 : 1 selectivity for 1° over 2° C(sp$^3$)–H bonds. Nevertheless, a 2° C(sp$^3$)–H bond of the cyclopropane ring could also be functionalized to afford tricyclic products. A pyrazole directed C(sp$^3$)–H olefination of the inherent alkyl group was reported by Yu and co-workers in 2016.[69] For the first time, they reported the use of an MPAA ligand in a palladium-catalysed C(sp$^3$)–H olefination reaction. The olefination reaction was compatible only with the tertiary alkyl group, however, diverse functional groups attached to the tertiary alkyl group as well as pyrazole ring were well tolerated under the given reaction conditions.

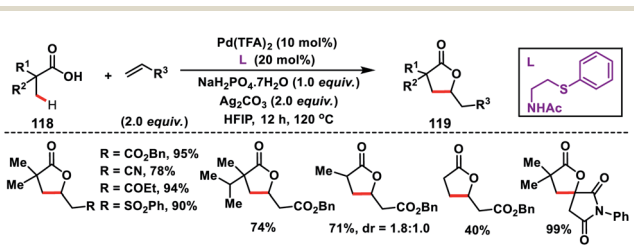
Yu group in 2018 established an inherent acid functionality as the directing group for β-C(sp$^3$)–H olefination without an auxiliary. They synthesized an MPAA ligand, *N*-Ac-protected aminoethyl phenyl thioether to carry out Pd(II)-catalysed β-C(sp$^3$)–H olefination of free carboxylic acids **118** (Scheme 59).[70] Subsequent lactonization of the olefinated product with acid yielded synthetically important γ-lactones **119**. It also limited the process towards being exclusively mono-selective in the presence of multiple β-C(sp$^3$)–H bonds. Substitution of other σ-donors in place of the sulfur atom led to a drop in the yield significantly, highlighting the importance of PhS. All the substrates provided the desired γ-lactones in good to excellent yield when coupled with activated alkenes. *N*-Arylated or *N*-alkylated maleimides were also found to be suitable coupling partners and afforded spirocyclic pyrrolidines.

To improve the generality of the olefination reaction with a variety of substrates Yu and co-workers developed a Pd(II)-catalysed β-C(sp$^3$)–H olefination of weakly coordinating intrinsic amides **120** (Scheme 60).[71] They utilized the weakly coordinating oxygen of amides as the directing group using pyridine-3-sulfonic acid based ligands. The observed olefination of the C(sp$^3$)–H bond was possible only in the presence of pyridine sulfonic acid ligands which indicated that the non-coordinating sulfonate group generates a highly electrophilic catalyst. For the viability of such transformations, there would be a charge separation between Pd and the ligand, which was supported by the complete inefficiency of pyridine-2-sulfonic acid. Apart from the diverse activated olefins, for the first time ethenesulfonyl fluoride, which is used in sulfur(VI) fluoride exchange (SuFEx) click reactions, was also utilized for the olefination reaction of the C(sp$^3$)–H bond.

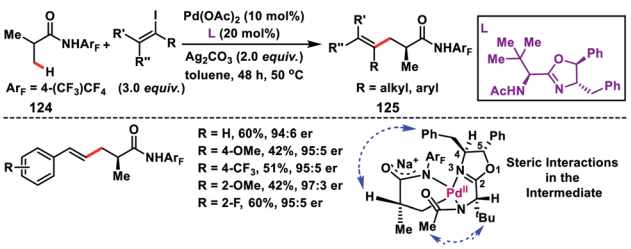
Complementary to C(sp$^3$)–H olefination with terminal olefins under oxidative conditions, C(sp$^3$)–H olefination could also be accomplished with vinyl halides without the requirements of any external oxidant. Such a Heck type reaction with C(sp$^3$)–H bonds proceeds through oxidative addition followed by reductive elimination involving PdII/PdIV akin to the PdII/Pd0 intermediate for terminal olefins. In 2014, Chen and co-workers developed a stereo-retentive installation of multi-substituted olefins *via* *N*-quinolyl carboxamide-directed olefination of the β-C(sp$^3$)–H of alanine amino acid **122** with alkenyl iodide (Scheme 61).[72] This strategy provided a path for the



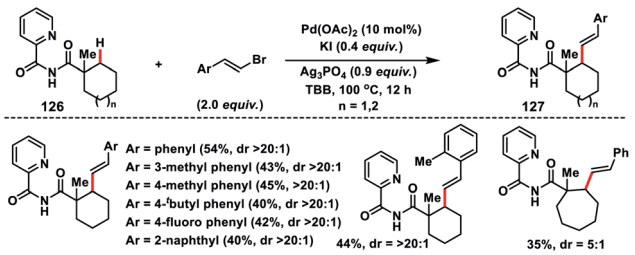

Scheme 61 Stereo-retentive olefination of the β-C(sp$^3$)–H bond of alanine with vinyl iodides.




Scheme 59 Ligand-enabled β-C(sp$^3$)–H olefination of free carboxylic acids.




Scheme 62 Pd-catalysed enantioselective C–H alkenylation of isobutyric acid.



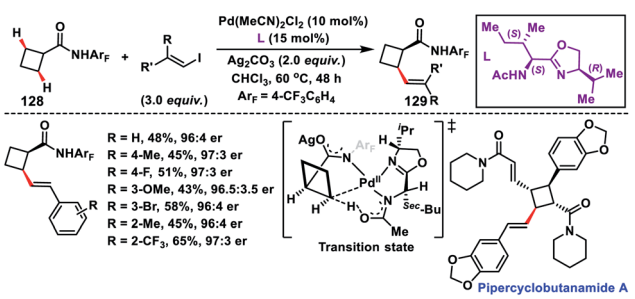

Scheme 63 Pd-catalysed β-C(sp$^3$)–H alkenylation with alkenyl bromides.

synthesis of a wide range of exciting β-olefinated α-amino acids **123**.

Yu and co-workers in 2017 demonstrated a Pd-catalysed enantioselective β-C(sp$^3$)–H olefination reaction of iso-butyric acid derived substrates **124** (Scheme 62).[73] The transformation provided a genuine route for the synthesis of some useful building blocks **125** with an enantioenriched α-chiral centre. Formation of a Pd–C–H intermediate was proposed, where the *N*-acetyl group of the coordinating nitrogen is directed towards the top face of the Pd square plane due to steric repulsion from the chiral centre on the side chain. There was a mutual relationship between the two stereocentres of the ligand as complete loss of enantioselectivity was observed when the absolute stereochemistry of one of the chiral centres was reversed. Furthermore, the 4-benzyl group of the oxazoline ring covers the top face of the intermediate. These combined steric interactions reinforced the orientation of the α-methyl group, thereby resulting in stereoselective cleavage of the C(sp$^3$)–H bond.

Later, Shi and co-workers developed 2-picolinamide as a new directing group for the Pd-catalysed β-C(sp$^3$)–H alkenylation of cyclic carboxylic acids **126** with alkenyl bromides (Scheme 63).[74] Interestingly, olefination reaction took place only at the secondary C(sp$^3$)–H bond instead of primary, which was in contrast to the arylation reaction on the same substrate. A wide range of alkenyl bromides were tolerated under the reaction conditions and provided the desired **127** in good yield and excellent distereoselectivity (>20 : 1).

Enantioselective olefination of the C(sp$^3$)–H bond of cyclobutyl carboxylic amides **128** was reported by Yu's group in 2018. The chiral mono-N-protected aminomethyl oxazoline (MPAO) ligand was used to obtain the desired products **129** in a moderate yield with good enantioselectivity (Scheme 64).[75a] The methodology was applied to synthesize diverse chiral cyclobutanes from simple monosubstituted cyclobutanes *via* sequential arylation and olefination. The precoordinated palladium acted as the active Pd(II) species which coordinated with amide and thus an enantio-determining C(sp$^3$)–H metalation took place creating a chiral Pd(II) intermediate. The foremost utilization of C(sp$^3$)–H olefination in the synthesis of the natural product pipercyclobutanamide A was reported by Baran and co-workers in 2015 (Scheme 64).[75b] They carried out an aminoquinoline directed Pd-catalysed alkenylation of an unactivated cyclobutane ring with alkenyl iodide. The transformation showed a glimmer of hope for the application of C(sp$^3$)–H olefination in natural products and synthesis of their derivatives.

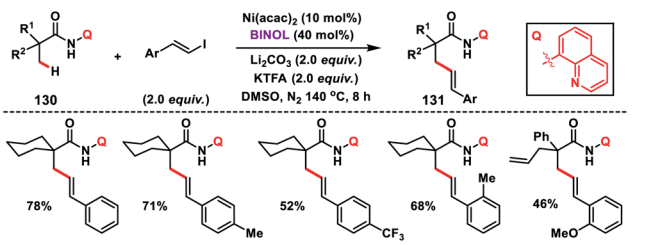



Scheme 64 Enantioselective C(sp$^3$)–H olefination of the cyclobutyl ring.

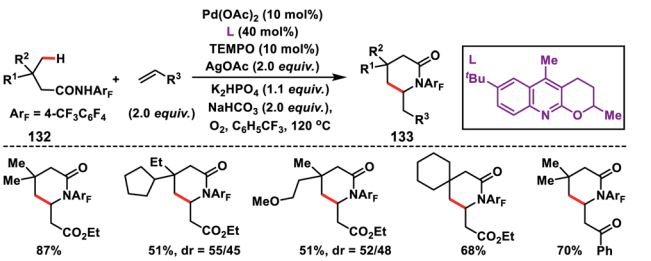
The first Ni-catalysed olefination of the β-C(sp$^3$)–H bond with alkenyl iodide was reported by Shi and co-workers in 2015 by using aminoquinoline as the bidentate directing group (Scheme 65).[76] The catalytic system employed in the transformation was an air stable Ni(acac)$_2$-catalyst and highly efficient BINOL ligand. A wide range of alkenyl iodides and carboxamides **130** bearing an α-quaternary centre were compatible and provided products **131** in good yield and selectivity. In the case of carboxamides having a cyclic system, olefination took place only at the primary C(sp$^3$)–H bond which was in contrast to the Pd-catalysed olefination reaction.

### 5.2. γ-C(sp$^3$)–H olefination

After the successful β-C(sp$^3$)–H olefination reaction, γ-C(sp$^3$)–H bond olefination was reported by Yu and co-workers in 2014 in order to generate a β-quaternary centre (Scheme 66).[77] They achieved γ-C(sp$^3$)–H olefination by employing a quinoline




Scheme 65 Ni-catalysed β-C(sp$^3$)–H alkenylation with alkenyl iodide.

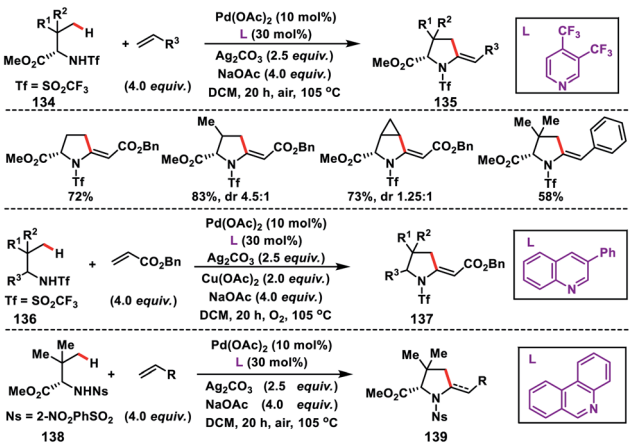



Scheme 66 Ligand-enabled construction of β-quaternary carbon centres.

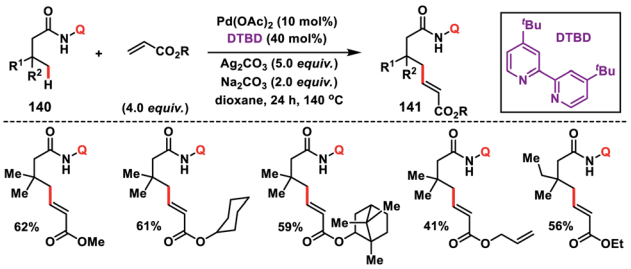
based tricyclic ligand and a weakly coordinating amide directing group **132** with a Pd-catalyst. The motive behind the use of quinoline based ligands containing a 2-alkoxy motif was that the lone pairs of oxygen constrained themselves to a plane parallel to the π-system of the quinoline ring. This resulted in higher electron density on the ligand which influenced the reactivity of the Pd(II)-catalyst. After extensive optimization, use of 10 mol% TEMPO as a co-oxidant in oxygen enhanced the yield of the product **133** significantly.

In 2016, Yu and co-workers developed another excellent approach for Pd(II)-catalysed γ-C($sp^3$)–H olefination of Tf- and Ns-protected amines. The olefinated intermediate underwent subsequent aza-Wacker oxidative cyclisation or conjugate addition to harvest a variety of C2-alkylated pyrrolidines.[78] They figured out three different classes of pyridine and quinoline based ligands to match the requirements for C($sp^3$)–H olefination of different classes of amines depicting a sporadic example of ligand enabled C($sp^3$)–H olefination. Interestingly, amino acids **134** containing both γ-methyl and γ-methylene C($sp^3$)–H bond, preferentially γ-methyl C($sp^3$)–H bond, were olefinated to **135** (Scheme 67). For α-amino acids the electron-deficient ligand 3,4-bis(trifluoromethyl)pyridine was effective to achieve the transformation. 3-Phenylquinoline was found suitable for the Tf-protected alkyl amines **136** including β-amino alcohols and afforded the desired products **137** in good yield (Scheme 67). The applicability of the strategy was further enhanced by the use of a common protecting group 2-nitrobenzenesulfonyl (Ns) in **138** instead of Tf with a different ligand phenanthridine (Scheme 67).

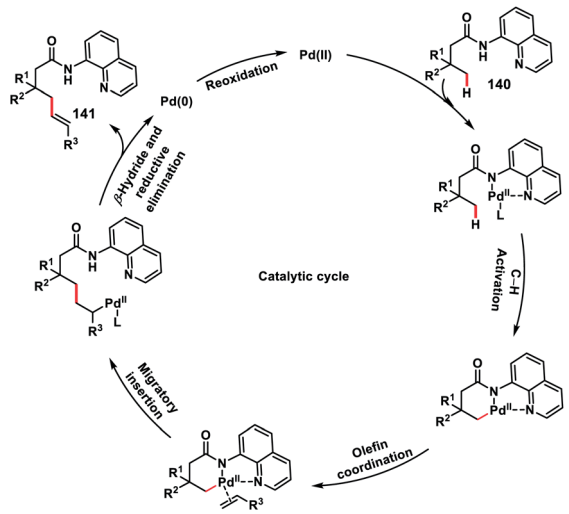
In 2017, our group developed a protocol for the Pd-catalysed γ-C($sp^3$)–H olefination of aliphatic acids **140** with activated olefins using 8-aminoquinoline as the directing group (Scheme 68).[79] The γ-C($sp^3$)–H olefination with acrylates occurred in the presence of a quinoline based ligand 4,4′-di-*tert*-butyl-2,2′-bipyridine (DTBD) along with Ag salt oxidant and $Na_2CO_3$ base. A variety of acrylates and acid derivatives provided the desired products **141** in good yield. Vinyl iodides were also equally compatible under the reaction conditions for the γ-C($sp^3$)–H




Scheme 67 γ-C($sp^3$)–h olefination of Tf and Ns-protected α-amino acids and alkyl amine.



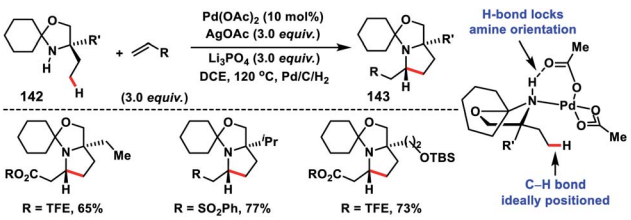

Scheme 68 Pd-catalysed γ-C($sp^3$)–H olefination with activated alkenes.



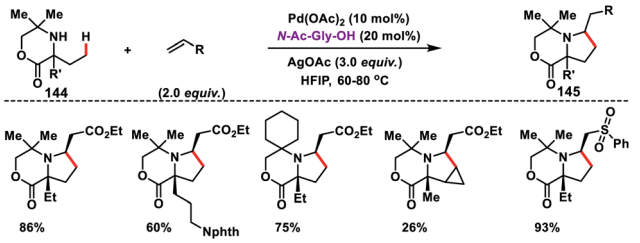

Scheme 69 Proposed mechanism for Pd-catalysed γ-C($sp^3$)–H olefination.

olefination of protected amino acids, however no ligands and external oxidants were required. This transformation occurred through the aminoquinoline-directed formation of a six-membered palladacycle intermediate. The olefin coordination followed by the migratory insertion of activated olefin and β-hydride elimination resulted in the final product and Pd(0), which was re-oxidized to Pd(II) with Ag(I) salt (Scheme 69).

In 2015, Gaunt and co-workers reported a Pd-catalysed γ-C($sp^3$)–H olefination of amino alcohols **142** followed by intramolecular aza-Michael addition to afford pyrrolidine moieties **143** in good yields (Scheme 70).[80] This transformation was achieved by the temporary conversion of the catalytically



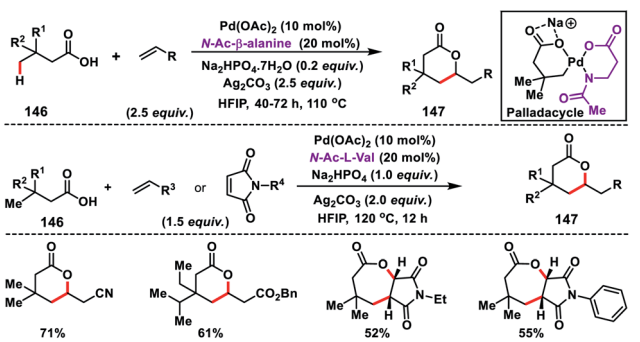

Scheme 70 Pd-catalysed γ-C($sp^3$)–H olefination of primary amino alcohols.



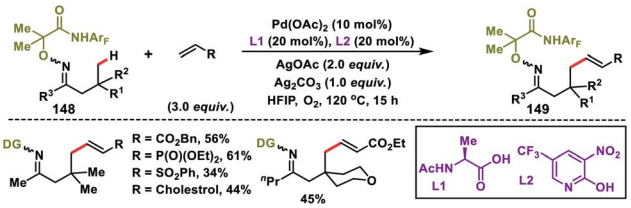

Scheme 71 Ligand induced γ-C(sp$^3$)–H olefination of aliphatic amines.

incompetent primary amino alcohol to a hindered secondary amine. The sterically hindered secondary amine was capable of promoting Pd-catalysed C–H activation reaction. The γ-C(sp$^3$)–H olefination reaction became feasible due to H-bonding between the catalyst and amine. This led to the intensive interaction of substrates around Pd and orientation of the aliphatic amine substituent in a perfect geometry needed for C–H activation. Later, Gaunt's group achieved a ligand assisted Pd-catalysed γ-C(sp$^3$)–H olefination of aliphatic amines **144** guided by the free (NH)-amine (Scheme 71).[81] A cyclopalladated five-membered ring formed, which allowed olefin insertion and aza-Michael cyclisation leading to pyrrolidine moieties **145** in good yields and excellent regio-and diastereoselectivity. They observed that the amino acid derived ligand strongly influences the C–H activation step for aliphatic amines containing the competitive sites of reactivity. By making the cyclopalladation step reversible, the ligand enables a productive five-membered cyclopalladation pathway.

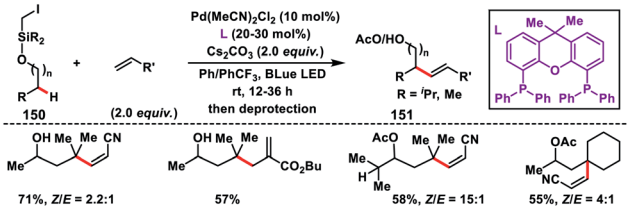
Gemmeren's group reported ligand assisted Pd-catalysed γ-C(sp$^3$)–H olefination of free carboxylic acids **146** without incorporating any exogenous directing group. The alkene intermediate followed an *in situ* intramolecular Michael addition to provide δ-lactones **147** in good yields (Scheme 72).[82a] Simultaneously, our group also demonstrated γ-C(sp$^3$)–H olefination of free aliphatic acids **146** under similar reaction conditions except the use of *N*-Ac-L-val-OH ligand instead of *N*-Ac-β-alanine (Scheme 72).[82b] Both δ-lactones and ε-lactones **147** were formed depending upon the olefin coupling partners. Six membered δ-lactones were formed when coupled with acrylates, ketones, nitriles and sulfones while ε-lactones resulted when




Scheme 72 Ligand-enabled γ-C(sp$^3$)–H olefination of free carboxylic acids.




Scheme 73 L,X-type directing group-assisted C–H olefination of ketones.




Scheme 74 Pd-catalysed radical relay Heck reaction.

coupled with N-substituted maleimides. It was worth noting that acids containing only a quaternary centre at the β-position were compatible which signify the Thorpe–Ingold effect. Mechanistic investigations suggested that the γ-C(sp$^3$)–H bond cleavage was the rate-determining step in the transformation.

Recently, Pd-catalysed γ-C(sp$^3$)–H olefination of weakly coordinating ketone derivatives **148** was reported by Yu and co-workers. They used a combination of mono-N-protected amino acid, electron-deficient 2-pyridone ligand and modified imino-amide L, X-type directing group (DG) for the purpose (Scheme 73).[83] The protocol has a wide scope of applicability and substituents on both ketones and olefins were well tolerated providing products **149** in moderate to good yield.

## 6. Miscellaneous

In 2019, Gevorgyan reported the unusual Pd-catalysed site-selective β-, γ- and δ-C(sp$^3$)–H olefination of alcohols **150** *via* radical relay Heck reaction under visible light at room temperature (Scheme 74).[84] The transformation took place at the sterically demanding site resulting in the formation of a quaternary carbon centre in the presence of Xantphos ligand. The strategy was compatible with a variety of alcohols and olefin substrates including styrenes and afforded the corresponding alkenylated products **151** in moderate to good yield. In substrates containing the competitive C(sp$^3$)–H site (*i.e.* β- *vs.* γ- and γ- *vs.* δ-), γ-C(sp$^3$)–H olefination took place preferentially due to the higher preference of 1,6-HAT (hydrogen atom transfer) for the Si auxiliary.

## 7. Conclusion and outlook

The Fujiwara–Moritani reaction opened a new avenue in the synthesis of olefinated compounds with excellent efficiency, economy and environmental benignity by the direct coupling of

C–H bonds. As discussed in the review, the last few decades of research demonstrated that irrespective of the nature of the C–H bond, transition-metal catalysts such as Pd, Rh, Ru, Ni, Co, and Ir made olefination reaction efficient and regioselective. Regioselectivity in the olefination reaction ($sp^2$ & $sp^3$) can be achieved by designing strongly as well as weakly coordinating directing groups along with the judiciary usage of a suitable ligand. Also, selective access of *meta*- and *para*-C–H bond was achieved by anchoring the covalently linked directing group which could form a cyclophane-like macrocyclic transition state. Very recently, researchers devised catalytic systems that enable nondirected C–H olefination reaction under arene limited conditions with broad substrate scope and improved selectivity. Site specific olefination in many medicinally important small heterocycles devoid of functional group to tether a template covalently can be achieved by designing bifunctional templates coordinated with two metal centres. Recent advancement in the asymmetric C–H activation resulted in an enantioselective C–H olefination reaction to access axially chiral biaryl compounds in a single step and atom economic way.

Despite these advances, oxidative C–H olefination reactions still face a number of challenges. For example, low regioselectivity is one of the major concerns. In some cases, this issue was addressed by the installation of the directing group. The poor selectivity in non-directed and distal C–H olefination limits its use in the bulk. Considering the practical importance of atom and step economical C–H bond olefination there are still many research areas left to be explored for the effective C–H olefination. Development of new traceless directing groups for the utilization of base metals such as Co, Ni, Cu and Fe under milder reaction conditions is one of the areas to be explored in the near future. New directions, such as use of frustrated Lewis ion pairs or acid–base pairs, are still unknown for remote $sp^2$ & $sp^3$ C–H bond olefination reaction. Often C–H olefination reaction requires high temperature which resulted in poor regio-selection leading to multiple site functionalization. Therefore, merger of metal/photoredox catalysis generally enabled the reaction to take place at room temperature ensuring higher regioselectivity. Another aspect of photoredox catalysis is that it avoids use of super-stoichiometric metal salts making the process more economical and environmentally benign. There is plenty of scope in photoredox C–H olefination reactions which remains to be explored especially for distal $sp^2$ & $sp^3$ C–H bonds. Recent development in the artificial metalloenzyme catalyzed asymmetric C–H functionalization opens a new avenue to be investigated for asymmetric C–H olefination reactions. Success in artificial metalloenzyme catalyzed asymmetric C–H olefination reactions will help to mimic the natural metalloenzyme and *in vivo* C–H olefination could be utilized for targeted drug delivery. Also, C–H olefination reaction of DNA encoding can lead to the formation of a DNA encoded library. Therefore, to find more applications in natural product synthesis, drug discovery and agrochemicals, further improvement in the C–H bond olefination is expected. To address these inadequacies, development of effective templates, catalysts, ligands and new approaches are required with the detailed understanding of the olefination mechanism.

## Conflicts of interest

There are no conflicts to declare.

## Acknowledgements

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