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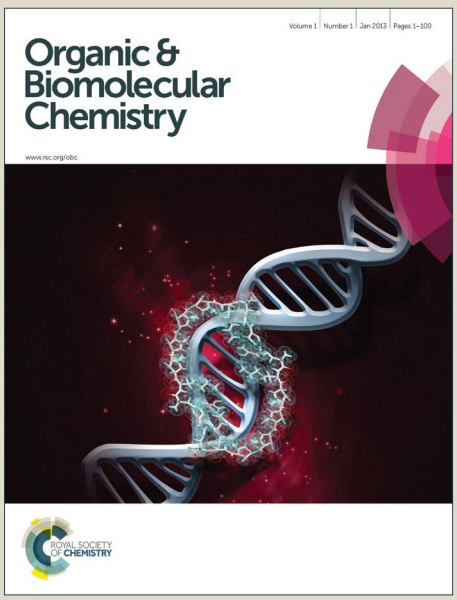

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REVIEW

Palladium catalysed *meta*-C–H functionalization reactions

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Directing group assisted site selective C–H functionalization approach is continuously impacting the field of natural product synthesis, drug discovery and material sciences. While *ortho*-selective C–H functionalization has been studied extensively, *meta*-selective C–H functionalization has been less explored. Recent studies have highlighted the efficacy of palladium as a catalyst in activating the *meta*- C–H bond of arenes. Notably, introduction of a novel palladium catalysed directing template based approach to activate *remote meta*- position has created a revolutionary impact in seeking a solution to this long standing challenge. In this review we summarize the recent advancements on palladium catalysed *meta*-C–H functionalization that helped in creating a new outlook towards modern organic synthesis.

1. Introduction

Functionalization of aromatic arenes constitutes an important phenomenon in organic synthesis with regards to their omnipresence in complex molecular entities. Organic molecules containing such functionalized aromatic nucleus pose to be significant in terms of their importance in pharmaceutical, material science, drug development and polymer chemistry. Consequently, a desired incorporation of functional groups fraught with an uncompetitive site selectivity serves as a paramount subsidiary[1-8]. With reference to the plausible sites of electrophilic attack, *ortho*- and *para*- substitution of aromatic arenes have been quite thoroughly explored by the aid of classical organic synthetic reactions since the past few decades. Attack on the *meta*-position however awaited much more scientific investigation since the *meta*-position in an aromatic arene is the least activated for a facile electrophilic substitution. Activation of the *meta*-position in an arene system was vital since this could pave the way for synthesis of several natural products, medicinal drugs, agrochemicals, *etc.* in which presence of functional groups suitably located at the *meta*- position impart them the required functional characteristics. An intense scientific research in conjunction with the chemistry of metal induced catalysis was subsequently envisioned for overcoming this challenge. Seminal works on metal catalysed (eg. Cu(II), Ru, etc.) *meta*- selective transformations[9-13] by Gaunt, Frost, Ackermann, Hartwig, and others emerged as a popular tool in organic chemistry owing to the vast applicative potential that these transformation could wield.

Literature reports in the past few years have proved the catalytic supremacy of palladium based salts in performing numerous carbon-carbon and carbon-heteroatom bond forming reactions.[14-16] A closer look at such organometallic transformations[17-20] comprehends mainly the Heck, Suzuki, Fujiwara-Moritani reaction, etc. Moreover, an imminent problem was to discern the desired selectivity during the execution of a functionalization at a target site of an aromatic ring since a carbogenic motif can have numerous vulnerable C–H bonds. A leap in this regard was made by the introduction of a palladium (II) catalysed directing group based *meta*-C–H activation strategy that rose to be of primordial distinction. This made possible to activate the *meta*-C–H bonds that are at a distal location relative to the existing functional groups and also overcome any possible steric and electronic bias. In this review, we revisit the significant advancements in palladium catalysed *meta*-C–H functionalization in a chronological order along with their wide synthetic utility in order to foster further scientific perception.

2. Scope of functionalization

Owing to the relatively short span of time in which palladium catalysed directed *meta*-C–H transformations have been developed, the scope of functionalization includes majorly olefination, acetoxylation, arylation, hydroxylation and more recently iodination. However, other functionalizations have also recently been reported in presence of other catalytic systems (*e.g.* ruthenium[21-23]). Herein, we remain mainly focussed on palladium catalysed directed *meta*-selective transformation. We shall discuss various aspects of the above transformations along with the design principles that led to the effective *meta*-C–H functionalizations. Moreover, we shall delineate the gradual evolution of the directing groups and how they were useful towards accomplishing such an admirable advancement in synthetic chemistry.

2.1 Olefination

The presence of innumerable functionally vulnerable C–H bonds within a molecule necessitated the development of a systemic protocol that could allow the required functionalization with distinguished site selectivity. Chelation assisted transformations had been found to be successful in performing selective *ortho*-C–H transformations including olefination, halogenation, amination, etc. Extension of such an approach towards performing *meta*-C–H functionalization was difficult since the distal location of the target bond forbidded the formation of a cyclic metallacycle.

A successful breakthrough in this regard was made by the Yu group in 2012 when they reported template assisted *meta*-C–H activation of arene-based substrates using a palladium (II) catalyst

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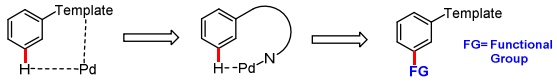
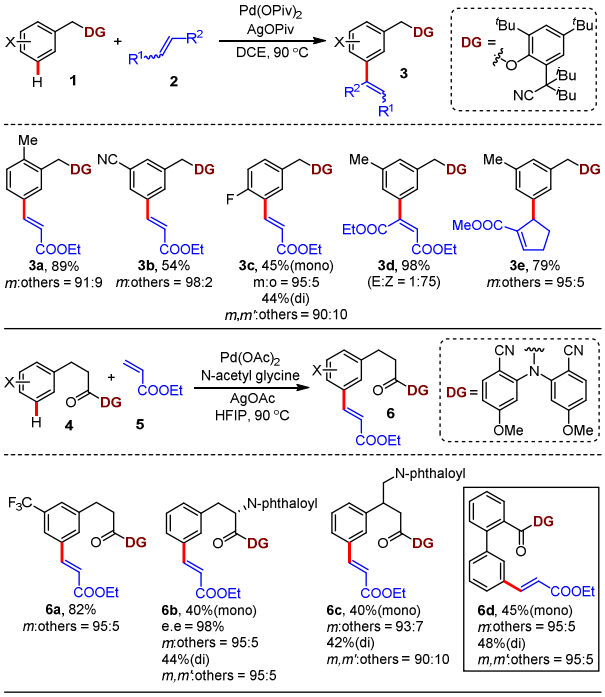
and *N*-acetyl glycine as ligand (Scheme 2).[24] This was the first ever report on a directing group mediated *meta*-C–H functionalization *via* formation of a 12-membered metallacyclic transition state. The design of the template was able to withstand the strain involved in formation of the metallacycle. It was able to deliver the coordinating donor moiety to a close proximity of the target *meta*-C–H bond and activate it. *Meta*-olefination of toluene, hydrocinnamic acid as well as 2-biphenylcarboxylic acid was obtained using a nitrile based directing template. Utility of the protocol was further demonstrated by the synthesis of derivatives of the drug Baclofen.



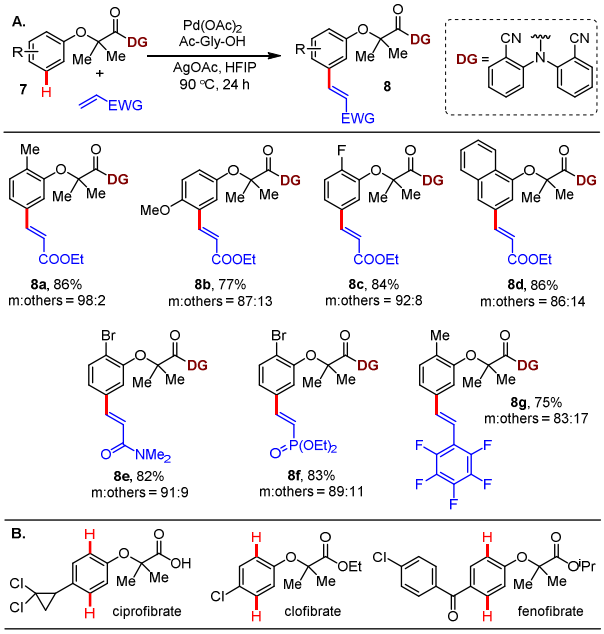
Scheme 1: Template directed *meta*-C–H activation

As far as aromatic electrophilic substitution is concerned, arenes containing electron-withdrawing group could only sustain electrophilic attack at the *meta*-position. This has been well



Scheme 2: Palladium catalysed directing group mediated *meta*-selective olefination of toluene, hydrocinnamic acid and 2-biphenylcarboxylic acid.

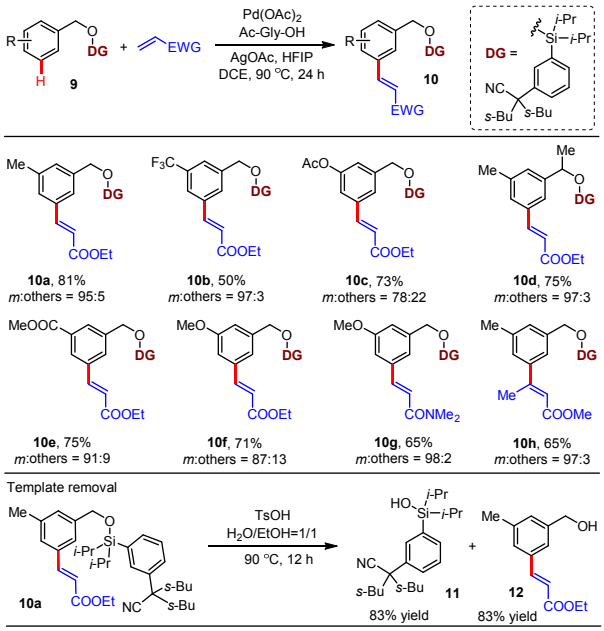
endeavoured through classical organic synthesis reactions in which electronically deficient arenes, say nitrobenzene, could undergo a



Scheme 3: A) Palladium catalysed directing group mediated *meta*-selective olefination of α-phenoxycarboxylic acids. B) Medicinally important drugs.

facile electrophilic attack at *meta*-position since the *ortho*- and *para*-positions remained unactivated owing to the electron withdrawing character of the directing functional group (*e.g.* NO_2 in nitrobenzene, COOH in benzoic acids, *etc.*). The year of 2013 witnessed *meta*-C–H activation of α-phenoxycarboxylic acids and their 2-bromo derivatives using a cyano containing directing group (Scheme 3).[25] This meant synthesis of drugs such as ciprofibrate, fenofibrate, etc. that contained α-phenoxycarboxylic acid core would be easier. Olefin scope showed the feasibility of styrene derivatives containing electron-withdrawing groups. Isotopic effect studies (k_H/k_D=3.8) suggested the cleavage of the C–H bond in the rate-determining step.

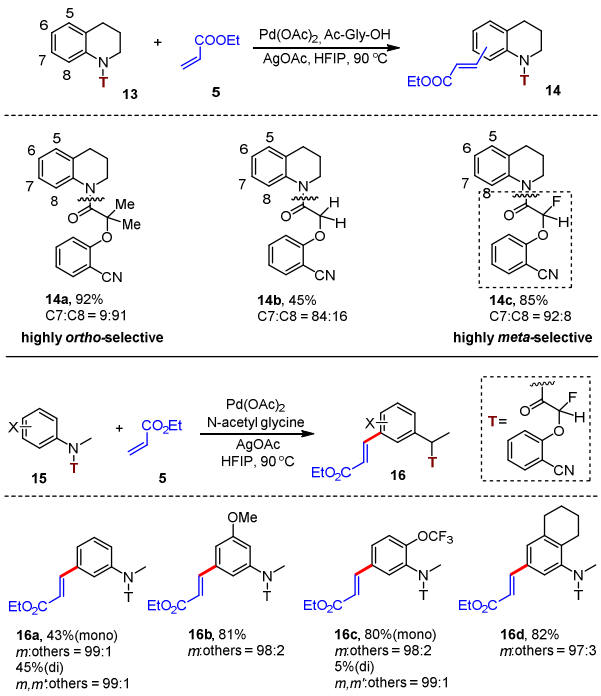
Later in the same year, Tan and co-workers presented a silyl-benzyl scaffold to perform a highly regioselective *meta*-C–H olefination facilitated by a palladium catalyst (Scheme 4).[26] The directing template had an edge over the directing groups[24, 25] discovered by Yu. Until now, carbonyl tether was used to link the target aromatic substrate with the directing group containing the metal coordinating donor moiety. Tan replaced this tether linkage by a bulky di-isopropyl substituted silicon centre[27-30]. Owing to the larger size of silicon and longer C–Si and Si–O bond, there was an increased proximity of the donor group to anchor the palladium metal close to the target C–H bond and its subsequent activation.



Scheme 4: Palladium catalysed *meta*-selective olefination using silyl-based scaffold.

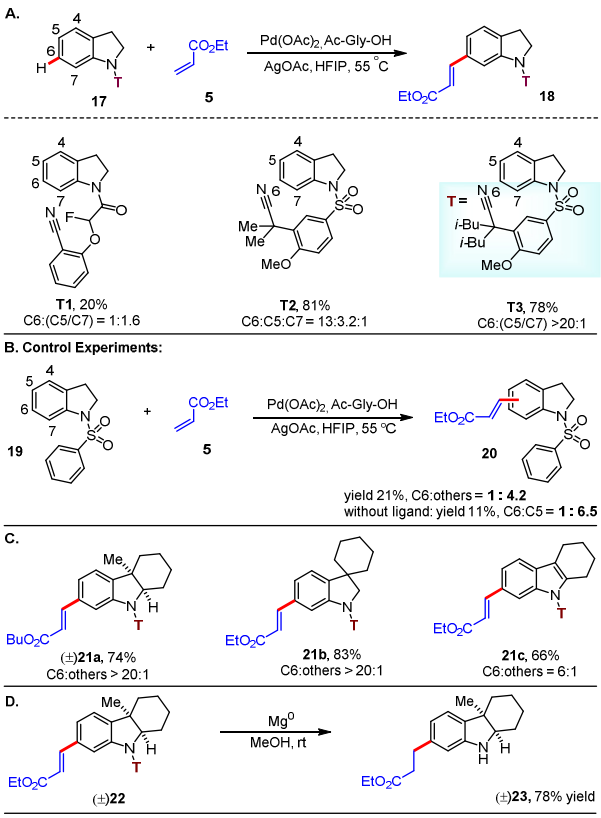
Moreover, presence of bulky groups installed at α-position of nitrile donor also facilitated *meta*-selectivity. Kinetic isotope effect of 2.5 was observed suggesting cleavage of C–H bond in rate determining step. Moreover, removal of the directing group was easy and could be performed under mild fluoride- or acid-catalysed deprotection conditions. These features served to be additional benefactors to promote late-stage functionalization and therefore a perfect adoption of the silyl based scaffold for *meta*- olefination.

In 2014, Yu group popularised *meta*-C–H olefination of tetrahydroquinolines and *N*-methylanilines (Scheme 5).[31] This was performed by employing a recyclable template that performs *meta*-selective functionalization of bicyclic heterocycle. This work emphasizes on the apt conformation of the directing template to be a necessity in targeting enhanced levels of *meta*- C–H selectivity. Presence of a suitably located fluorine substituent[32, 33] in the template allows for a switch from *ortho*- to *meta*- selectivity in presence of the ligand Ac-Gly-OH. This is because the installed fluorine atom could lower the rotational barrier of the amide N–C bond thus allowing the carbonyl group to be oriented away from the target bond and the nitrile donor to remain closer to the *meta*-C–H bond. Nullifying both steric and electronic bias, *meta*-selectivity ranged from 94% to 99%.



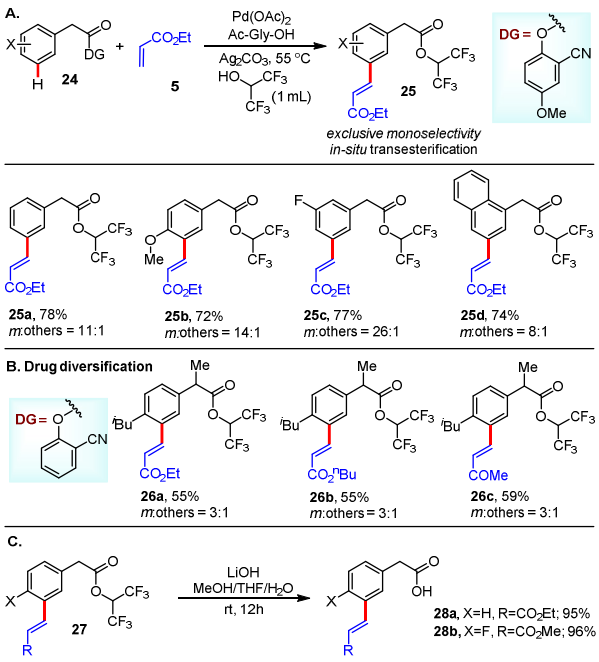
Scheme 5: Palladium catalysed directing group mediated *meta*-selective olefination of tetrahydroquinolines and *N*-methylanilines.

In the following year of 2014, Yu reported *meta*-selective olefination (*meta:* C5/C7, >20:1) of indoline based derivatives by nitrile containing end-on templates (Scheme 6).[34] The previously reported templates, suitable for performing *meta*-activation in phenols, anilines and tetrahydroquinolines, failed in ensuring promising *meta*-selective functionalization of indolines. This is because of the increased electron-donating ability of the nitrogen atom within the indoline system. The formerly discovered templates could not override this intrinsic *ortho*- and *para*- electronic bias. This necessitated the installation of a template that will be appended to the target substrate by an electronically withdrawing sulphonyl group since it can reduce the electronic bias within the indoline system created by the nitrogen atom of the cyclic ring. Incorporation of alkyl groups at the α-position of nitrile group further brought in the Thorpe-Ingold effect in order to allow closer approach of end-on nitrile donor towards the target *meta*- C–H bond. Functional tolerance was further explored. Removal of the template occurred at room temperature by magnesium turnings in methanol, which could simultaneously lead to reduction of the installed olefins and finally furnish *meta*-alkylated substrates.

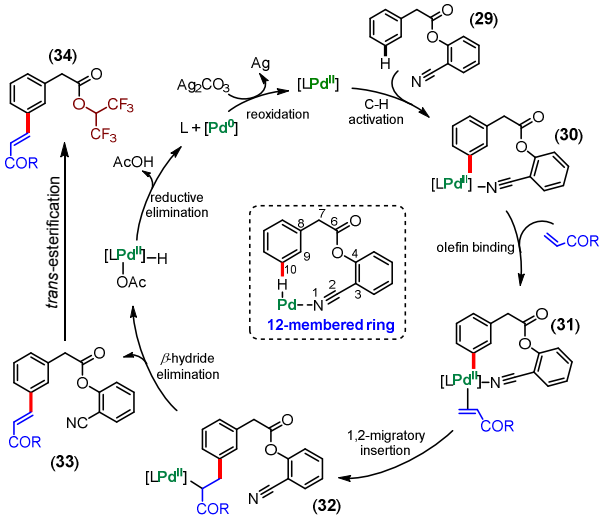


Scheme 6: A) Palladium catalysed directing group mediated *meta*-selective olefination of indolines. B) Control experiments. C) Substrate scopes. D) Template removal and reduction of alkene to alkane.

In the subsequent months of the same year, Maiti presented *meta*-selective olefination (Scheme 7) on synthetically and medicinally useful phenylacetic acid derivatives.[35] In this case, 2-hydroxybenzonitrile was used as the directing template. The approach proved to be novel in terms of the fact that the directing template was easy to install and then remove. Moreover, there was exclusive formation of the *meta*-olefinated product without competitive formation of any di-olefinated products. HFIP was used as a solvent along with introduction of methoxy group at the *para*-position of 2-hydroxybenzonitrile to decrease the percentage of transesterification[36]. This lead to increase in the yield of mono-olefinated product to nearly 78%. Substrate scope comprised of screening several olefin partners as well as electron withdrawing/electron donating group substituted derivatives of the phenyl ring as well as naphthylacetic acid derivatives. Hydrolysis of the template was performed at room temperature with LiOH. This protocol was further extended to ibuprofen, an antipyretic and analgesic drug, which demonstrated the applicability of the transformation in drug development and diversification. In the presence of the weakly coordinating nitrile donor in the directing template that anchors palladium center selectively towards the *meta*-position, a 12 membered cyclophane like pre-transition state was proposed (Scheme 8). The subsequent steps involve C–H activation, olefin binding, 1,2 migratory insertion and *β*-hydride elimination.[37] A facile transesterification then afforded the desired product.



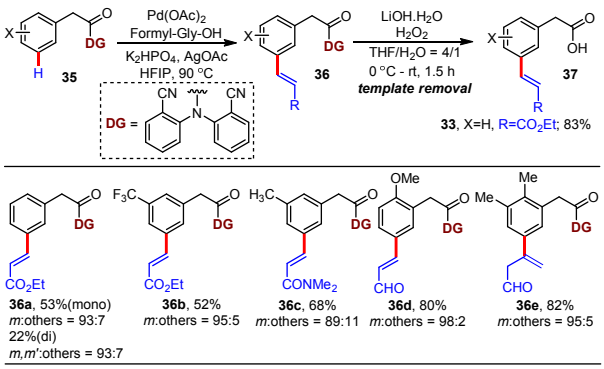
Scheme 7: A) Palladium catalysed directing group mediated *meta*-selective olefination of phenylacetic acids by Maiti and coworkers. B) Drug diversification. C) Template removal.



Scheme 8: Proposed catalytic cycle

Subsequently, Yu and coworkers also reported *meta*-olefination of phenylacetic acid derivatives (2015).[38] In this work, they showcased the effectiveness of *N*-formyl protected glycine (Formyl-Gly-OH) ligand and an additive such as KH_2PO_4 to be important for the reaction with HFIP as solvent, $Pd(OAc)_2$ as the catalyst and Ag_2CO_3 as the oxidant (Scheme 9). *Meta*- olefinated products were obtained with good selectivity (*meta*:others, 91:9) with upto total yield of 76% (mono:di, 3:1). Presence of a base like KH_2PO_4 was helpful in promoting the bidentate ligand coordination. From the available observations, displacement of the nitrile group by the olefin was thought to occur prior to the migratory insertion step. Until then, acrolein (*α,β*- unsaturated aldehyde) was used for C–H

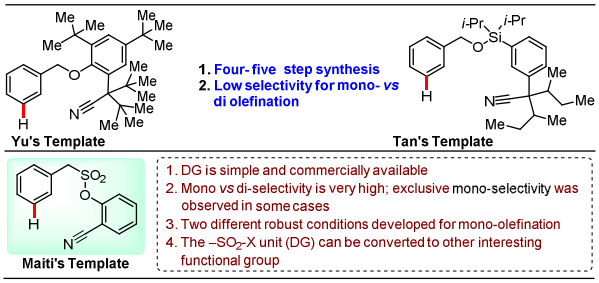
olefination only through non-directed approaches as demonstrated by Backvall[39], Lee[40] and Ishii[41].



Scheme 9: Palladium catalysed template directed *meta*-olefination by Yu and co-workers.

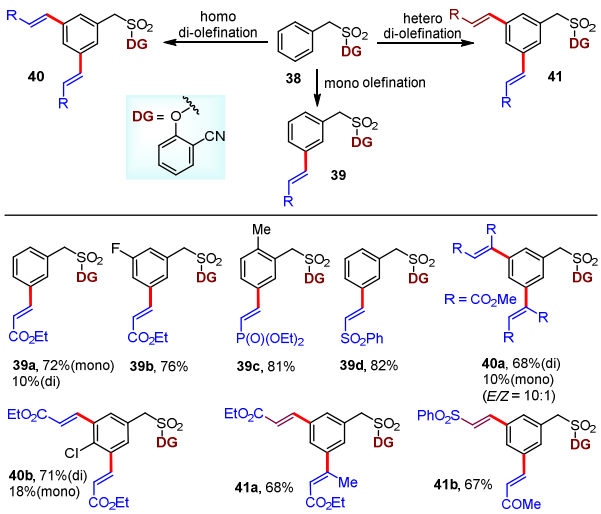
In 2011, Gevorgyan and coworkers had provided an example of using acrolein in a silanol directed *ortho*-C–H alkenylation[27] in phenols. An important achievement in this work therefore was the exhibition of acrolein and meta acrolein (**36d**, **e**) as effective olefin partners for template directed *meta*-C–H olefination. However, presence of bromo or iodo substituents in the phenyl ring of the arylacetic acid was found to be incompatible for the reaction. Removal of the template was performed with $LiOH/H_2O_2$ at room temperature[42].

In the same year (2015), Maiti introduced a novel strategy in performing *meta*- selective homo-diolefination and sequential hetero-diolefination of benzylsulphonylester derivatives (Scheme 10).[43]

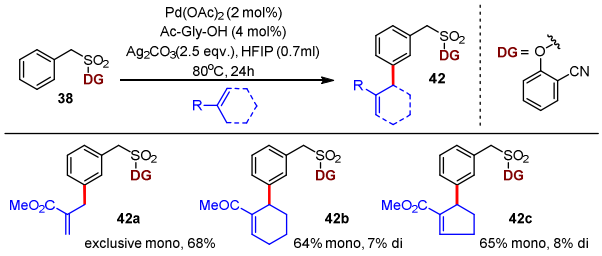


Scheme 10: Preferential advantage of Maiti's template over Yu and Tan's

Previously *ortho*- selective C–H olefination of benzyl sulphonamides[44] and *ortho*-selective hetero-diolefination[45, 46] have been duly reported, however hetero-diolefination at the *meta*-position remained unexplored. Owing to the synthetic importance of divinylbenzene derivatives[47, 48] and difficulty in synthesizing these by conventional approaches, this work proved to be of extreme significance. Sulphonyl tether was helpful in providing flexibility for the directing group to reach out to the target *meta*- site. Moreover, the directing group was simple and commercially available. This provided an additional edge over the directing groups used by Yu and Tan since the synthesis of their directing groups required multiple steps. Also, an easy removal of the directing group under mild condition, such as KOH in methanol at room temperature, proved to be pretty advantageous. Hetero-diolefination was performed by sequential addition of two different olefins in a one-pot process (Scheme 11). Further, mono-olefination at the *meta*-position was also exhibited with a decreased amount in the catalyst loading, *i.e.* 2 mol% palladium catalyst in HFIP solvent. Reaction with methacrylate and cyclic trisubstituted olefins proceeded to provide meta-selective monoallyl benzene derivatives in good yields (Scheme 12). Formation of these allyl benzene derivatives could be

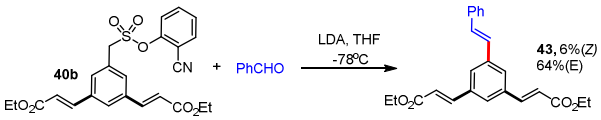


Scheme 11: Palladium catalysed *meta*-selective mono, homo di- and hetero di- olefination of benzylsulphonyl based scaffolds.



Scheme 12: Formation of *meta*-allyl benzene

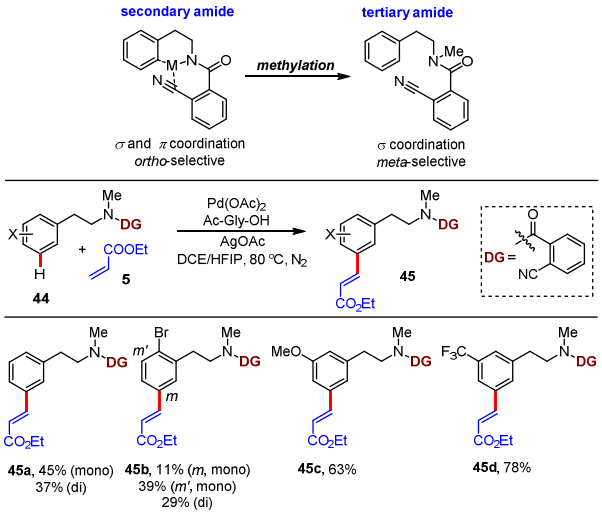
explained by the regioselective β-H_b elimination rather than β-H_a elimination.[49] Kinetic studies revealed the first order rate dependency on **38** for di-olefination. Cleavage at the sulphonyl group after di-olefination could also be performed by Julia olefination thus allowing synthesis of tris-(olefinated) benzene derivatives **43** (Scheme 13).



Scheme 13: Synthesis of tri-olefinated arene.

Following this, Li and coworkers reported palladium catalysed template directed *meta*-C–H olefination of phenethylamines through a regiodivergent functionalization protocol (Scheme 14).[50] Here, 2-cyanobenzoyl motif was employed as the directing group which could perform *remote-selective* olefination at *ortho*- and *meta*-C–H bonds of phenethylamine by utilizing both σ and π coordinating ability of the nitrile group in presence of a palladium (II) catalyst. Using analogous template anatomy, they performed selective remote

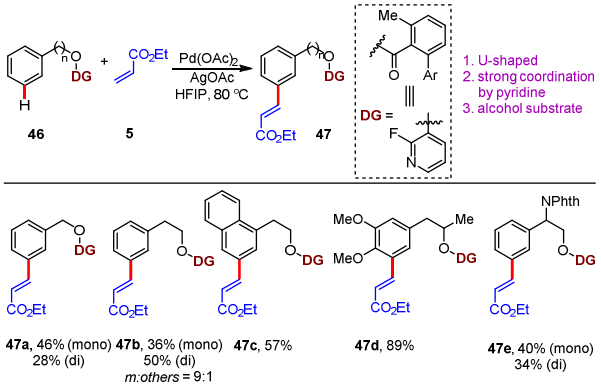
ortho-olefination leaving the proximal *ortho*-C–H bond. Treatment of ethyl acrylate in presence of $Pd(OAc)_2$ as catalyst, *N*-acetyl glycine as ligand and HFIP as an additive, selective remote *ortho*-C–H olefination was



Scheme 14: Palladium catalysed template directed *meta*-C–H olefination of phenethylamines through a regio-divergent functionalization protocol.

observed under aerobic condition. This was found to proceed through cyclization of the cyanobenzoyl motif to an imidamide derivative. Following *ortho*-olefination, methylation at the secondary amide lead to the formation of a tertiary amide linkage between the appended phenylethylamine and cyanobenzoyl. Under the optimized condition with $Pd(OAc)_2$ as the catalyst, *N*-acetyl glycine as the ligand coupled with a combination of dichloroethane and HFIP, selective *meta*-olefination was obtained with a combined yield of nearly 90% (mono:di, 46:44) under nitrogen atmosphere. Electronic bias was successfully overridden as was observed from the *meta*-olefination of the 3-methoxy substituted arene derivative. The only drawback of this work was the inability to alleviate the formation of the di-olefinated product as a side reaction.

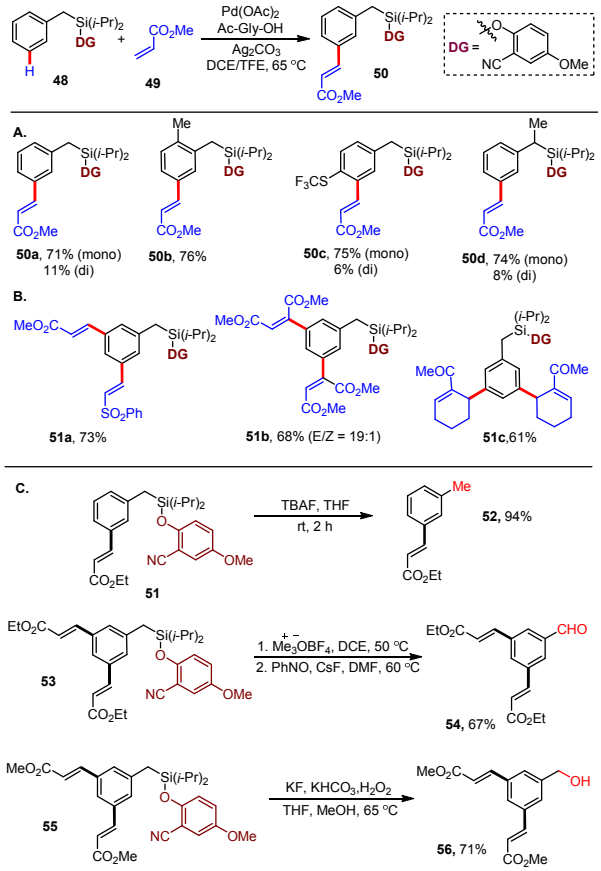
Even after three years since its discovery, the reported protocols for directing group mediated selective *meta*-C–H functionalization utilized weakly coordinating nitrile donor. Replacing nitrile donor with a strong coordinating group[51, 52] seemed to be a potential



Scheme 15: Palladium catalysed template directed *meta*- C–H olefination of benzyl and phenylethyl alcohols using 2-fluoropyridine based scaffolds.

approach to allow varied classes of functionalization. This was attempted by the Yu group in 2015 by superseding the nitrile donor with a 2-fluoropyridine based directing group where lone pair of the pyridine nitrogen will simulate end-on coordination of nitrile.[53] Subsequently, palladium (II) catalysed *meta*-olefination was performed with the pyridyl based directing group attached to benzyl and phenylethyl alcohols. Functional group tolerance was duly exhibited along with successfully overriding both steric and electronic bias (Scheme 15).

Maiti reported the *meta*-selective mono and bis-olefination of benzyl silanes using a weak nitrile containing directing group in early 2016 (Scheme 16).[54] A remarkable yield of nearly 84% for mono *meta*-selectivity (>20:1 and mono:di, 7:1) was obtained using 2-hydroxy-5-methoxybenzonitrile as the directing group with lower catalyst and ligand loading. The additional advantages included

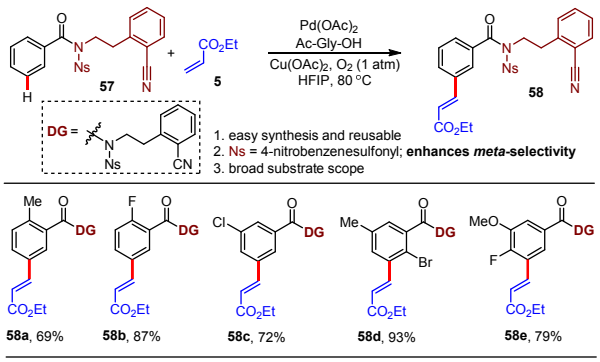


Scheme 16: Palladium catalysed template directed (A) *meta*- mono-olefination (B) *meta*- di-olefination (C) late-stage functionalization, by Maiti's benzylsilyl scaffold.

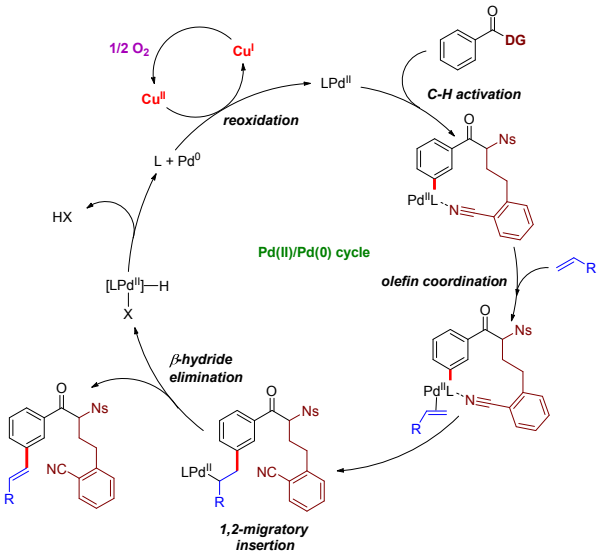
an easy commercial availability, versatility of the silyl linker, simple installation and removal of silyl linker. Synthesis of divinylbenzene derivatives was important owing to their importance in materials research and synthetic chemistry. A sequential bis-olefination at *meta*-position proved to be useful in this regard. Moreover, significant beneficial factors were vested with an easy late-stage modification of the C–Si bond under various conditions. Thus, formation of *meta*-olefinated toluene, benzaldehyde and benzyl

alcohols was duly conceived. Formation of a deuterium substituted toluene derivatives was also reported by using methanol-d_4 at the time of silanol deprotection.

Traditional aromatic electrophilic substitution reactions used harsh conditions for functionalizing the *meta*-position of benzoic acid derivatives which remain deactivated to these reactions. In particular, transition metal catalysed *meta*-functionalization of benzoic acid had remained unsuccessful. Recently in 2016, Li and coworkers have reported a palladium catalysed *meta*- olefination in these low reactive electron poor benzoic acid derivatives with cyano-directing template containing a suitably placed nosyl group (Scheme 17).[55] Presence of the nosyl group facilitated enhanced *meta*-selectivity. This protocol introduced the feasibility of oxygen as the terminal oxidant in presence of a catalytic amount of $Cu(OAc)_2$ (Scheme 18). Excellent yields (92%; mono:di, 1.1:1) of *meta*-olefinated products were obtained in presence of Ac-Gly-OH at 90 ^oC for 48h. This demonstrated the replacement of the conventional silver salt in all previously reported chelation-assisted *meta*-C–H olefination. Additionally, use of Formyl-Gly-OH in presence of inorganic bases like KH_2PO_4 or K_2HPO_4 yielded a good ratio of mono over di-olefination. Importance of the protocol was shown by the synthesis of an aspirin derivative *via* homo-diolefination.



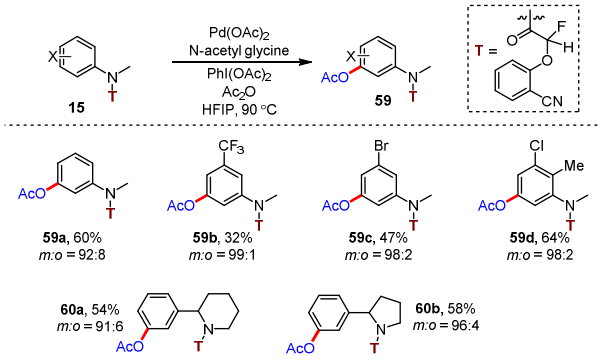
Scheme 17: Palladium catalysed template directed *meta*-C–H using silylbenzyl based scaffolds



Scheme 18: Palladium catalysed template directed *meta*-C–H olefination using Cu(II)/O_2 as terminal oxidant.

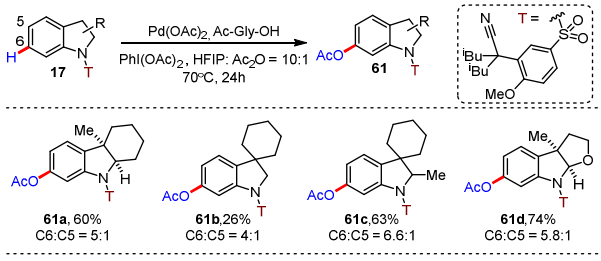
2.2 Acetoxylation

The versatility of palladium catalysed directing group assisted *meta*-C–H functionalization was explored in terms of formation of C–heteroatom bond as well. In this regard, implementing the protocol with an aim of forming *meta*-selective carbon-oxygen bond was a remarkable feat. After two years since the discovery of the innovative directing group assisted *meta*-C–H activation protocol, *meta*-selective acetoxylation was achieved using a palladium catalysed directing group assisted transformation. Catalysed by palladium acetate, using Ac-Gly-OH as the ligand $PhI(OAc)_2$ as the acetoxylating agent with a solvent combination of HFIP and acetic anhydride (10:1), selective *meta*-acetoxylation of *N*-methylanilines along with cyclic and acyclic benzylamine was successfully executed by Yu and coworkers in the year of 2014.[31] Moreover, *meta*-selective acetoxylation of 2-2-phenylpiperidine **60a** and phenylpyrrolidine **60b** was also executed enabling the synthesis of heterocycles of medicinal significance (Scheme 19).



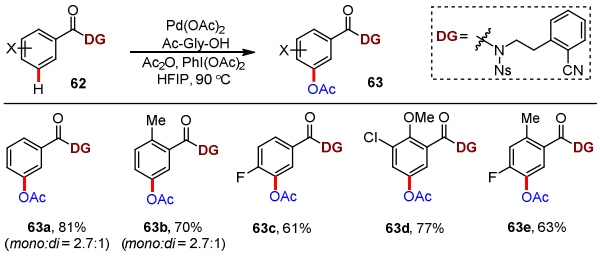
Scheme 19: Palladium catalysed template directed *meta*-acetoxylation of *N*-methylanilines and benzylamines.

Subsequently, in 2014, a promising attempt was made in performing palladium-catalysed *meta*-acetoxylation of indolines using the sulphonyl-based scaffold. *Meta*-hydroxylated indolines possess immense biological significance[56-58]. In this case also, 2 equivalents of $PhI(OAc)_2$ was used for acetoxylation. However, some amount of *para*-acetoxylation was also observed owing to the electron richness at the C5 position of the indoline (Scheme 20).



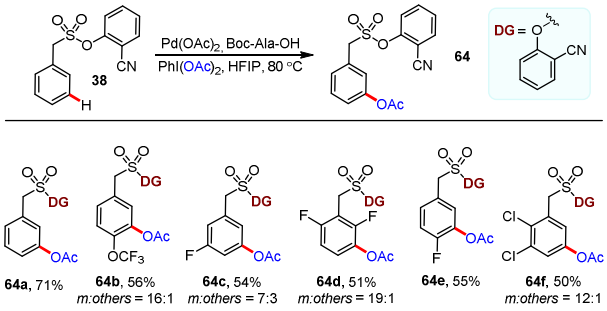
Scheme 20: Palladium catalysed template directed *meta*-acetoxylation of indolines

Following a similar reaction condition but under nitrogen atmosphere, Li and coworkers exhibited *meta*-selective acetoxylation on extremely low reactive benzoic acid systems using the nosyl containing sulphonamide based directing group. This recently reported[55] (2016) transformation (Scheme 21) was extremely useful as it enabled synthesis of several functionalized molecules containing a benzoic acid core owing to the easy removal of the directing group under mild basic conditions.



Scheme 21: Palladium catalysed template directed *meta*-acetoxylation of benzoic acids.

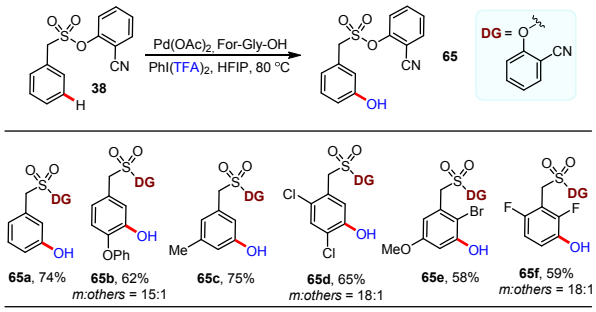
Recently, Maiti reported acetoxylation of benzenesulphonyl scaffolds using $PhI(OAc)_2$ and palladium acetate as the catalyst and *N*-*tert*-butyloxycarbonyl-alanine (Boc-Ala-OH) as ligand source.[59] However, we shall shortly discuss how a change of $PhI(OAc)_2$ to $PhI(TFA)_2$ lead to a novel transformation of facilitation a one-step hydroxylation phenomenon (See **2.3**, Hydroxylation). Nevertheless, formation of acetoxylated product was justified by the reduced electrophilicity of ester carbonyl in acetate that disfavoured hydrolysis. This was further corroborated by detailed computational studies (Scheme 22).



Scheme 22: Palladium catalysed template directed *meta*- acetoxylation of benzenesulphonyl scaffold.

2.3 Hydroxylation

Meta-acetoxylation of anilines, benzyl amine and indolines were reported. However, a selective one-step *meta*-hydroxylation reaction awaited revelation. Maiti presented the first report on such a benign transformation in early 2016, using a benzylsulphonyl ester (Scheme 23).[59] This was observed with $PhI(TFA)_2$ as the hydroxylating reagent with *N*-formyl glycine and $Pd(OAc)_2$ as the catalyst in HFIP solvent which yielded *meta*-hydroxylated product with an exquisite selectivity ratio of 32:1. Kinetic isotope studies confirmed C–H activation as the rate-determining step of the reaction. A first order rate dependency on palladium and substrate was obtained followed by a zero order dependency for $PhI(TFA)_2$.

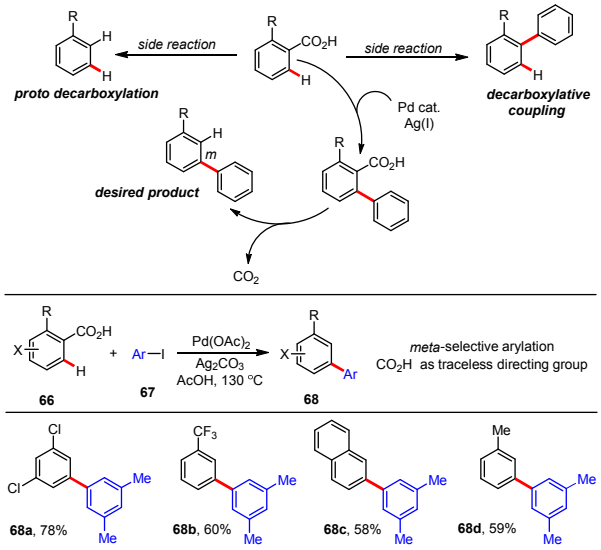


Scheme 23: Palladium catalysed template directed *meta*-hydroxylation and acetoxylation of benzenesulphonyl scaffold.

The difference in ligand environment, competitive co-ordination with the –CN and hindered deprotonation of the phenol under the mildly acidic conditions of the reaction mixture reduce the scope for undesired functionalization of the product.

2.4 Arylation

Development of a *meta*-arylation protocol would be a useful feat allowing diverse choices for retrosynthetic disconnections in biaryl synthesis. In this regard, *meta*-selective arylation has been pioneered by Gaunt[9] in 2009. However, it depended on

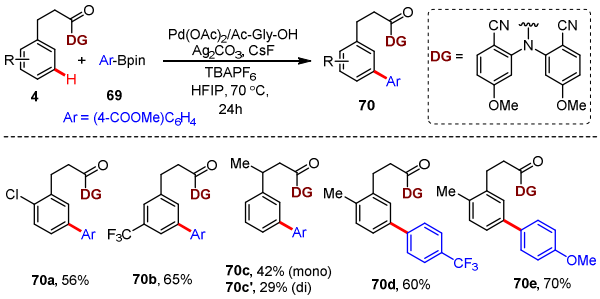


Scheme 24: Palladium catalysed *meta*-arylation using CO_2 as traceless directing groups.

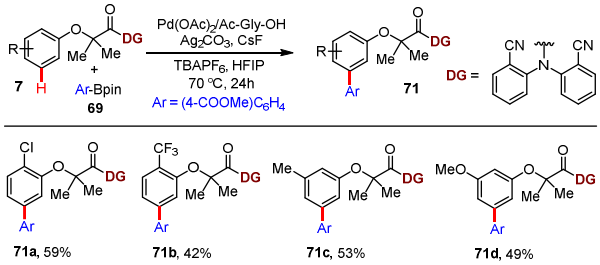
the exclusive use of 2-oxo-substituted directing groups and included Ar_2IOTf as a non-commercial coupling partner. In 2011, Larossa reported a formal *meta*- selective C–H arylation protocol using carboxylic acids as traceless directing group (Scheme 24).[60] This method proceeded through a tandem C–H arylation/protodecarboxylation pathway in presence of $Pd(OAc)_2/Ag_2CO_3$ as the catalyst/ligand combination. This method utilizes iodoarenes as the coupling partners along with benzoic acid, which is a cheap starting material. Importantly, this strategy could override possible electronic bias and provide perfectly regioselective coupling irrespective of the nature of the substituents present on the arenes. Proto-decarboxylation under Ag-catalysis with benzoic acids proceeded even on replacement of electron-withdrawing groups at

the *ortho*-position with electron-donating groups. Importantly, *meta*-arylation occurred on *ortho*-toluic acid **66d** which contained neither electron-withdrawing nor electron-donating substituents at the *ortho*-position.

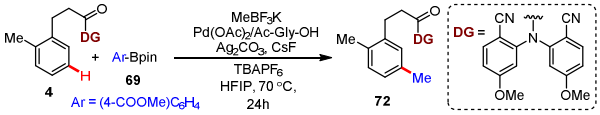
In 2013, Yu further exploited this template-based strategy in promoting palladium catalysed cross-coupling reactions of aryl boronic acids with *meta*-C–H bonds of aromatic arenes (Scheme 25,26).[61] This was made possible by the suitable choice of mono-protected amino acid (MPAA) ligands that was found to be effective during C–H coupling reactions with organoborons. A concoction of $Pd(OAc)_2$/Ac-Gly-OH/Ag_2CO_3/CsF/$TBAPF_6$ and arylboronic ester yielded the mono (yield, 48%) and di (yield, 35%) arylated product with 3-phenylpropanoic acid. This would make easier choices of retrosynthetic disconnections for formation of biaryls. Moreover, an interesting example on *meta*-methylation was presented using $MeBF_3K$ as the active methylating agent (Scheme 27).



Scheme 25: Palladium catalysed template assisted *meta*-arylation of hydrocinnamic acids.

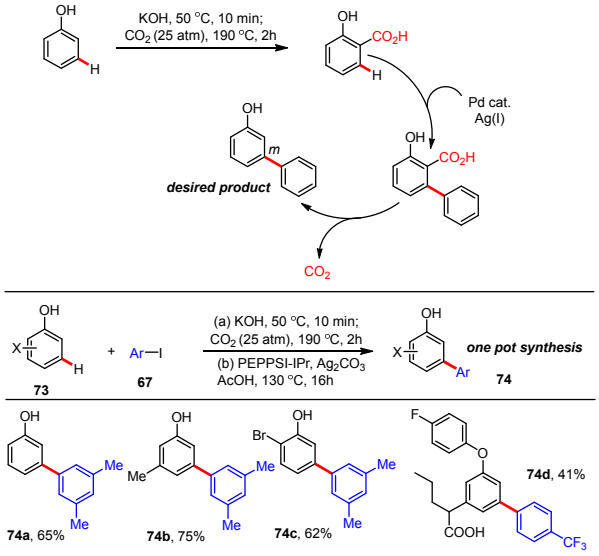


Scheme 26: Palladium catalysed template assisted *meta*-arylation of *α*-phenoxycarboxylic acids.



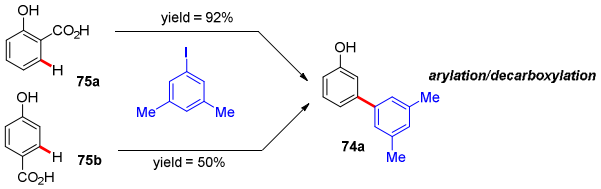
Scheme 27: Palladium catalysed template assisted *meta*-methylation.

In 2014, a one-pot direct *meta*-functionalization of phenols using iodoarenes as coupling partner was executed that involves the use of CO_2 as a traceless directing group (Scheme 28).[62] This was beneficial over Yu's directing template mediated arylation strategy which required independent synthetic reactions for their preparation.



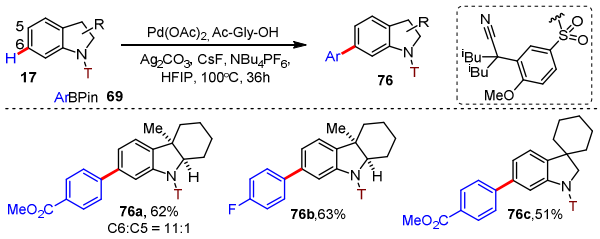
Scheme 28: Palladium catalysed *meta*-arylation of phenols.

Following a Kolbe-Schmitt carboxylation, the hydroxyl group imparted directing ability to the formed carboxylate. A tandem arylation/decarboxylation process was then initiated leading to the formation of *meta*-arylated phenols using 2mol% of PEPPSI-IPr and 0.5 equivalents of Ag_2CO_3. This was followed by complete removal of carbon dioxide. An *in situ* deprotonation and carboxylation of phenol was performed to develop a simple one-pot process. This eliminated the need of phenoxide formation which was a conventional pre-requisite for Kolbe-Schmitt carboxylation. Substrate scopes demonstrated a facile arylation even in the presence of aldehyde functionality without the requirement of any protection/deprotection. Applicability of this protocol was shown by a three step synthesis of a *γ*-secretase inhibitor **74d** (being monitored for treatment of Alzheimer's disease) from 3-bromophenol. Further mechanistic investigation was performed with 2- and 4-hydroxybenzoic acids formed by carboxylation of phenols (Scheme 29). Both molecules underwent successful *meta*-arylation indicating the ability of COOH to perform arylation at the *meta*-position independent of the initial carboxylation regiochemistry. However, the protocol failed in cases of increased steric bulk at the *para*-position of phenol or in cases of *ortho*-substituted iodoarenes.



Scheme 29: Mechanistic investigation by Larossa and coworkers.

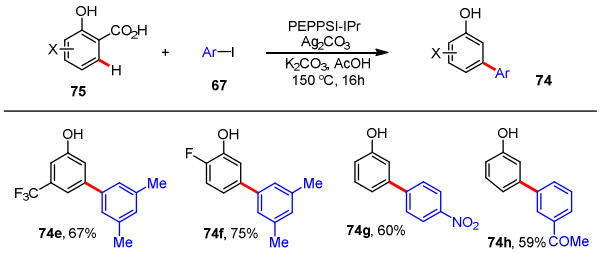
Meta-arylated indolines are important targets from the point of view of medicinal chemistry (Scheme 30).[63, 64] In 2014, using the sulphonyl based scaffold with nitrile as a donor group, selective *meta*-arylation was exhibited with arylboronic acid pinacol esters in synthetically useful yields.[34] Significance of a fluoride source was found to be important in the transmetallation step for



Scheme 30: Palladium catalysed template assisted *meta*-arylation of indolines.

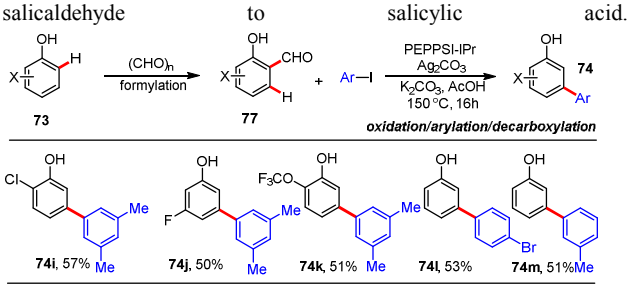
activation of boronic acid ester.[19] Using a suitable combination of palladium acetate (catalyst), Ac-Gly-OH(ligand), silver carbonate (oxidant), CsF and NBu_4PF_6, *meta*-selective arylation was performed on indoline derivatives.

In 2015, Larossa demonstrated the feasibility of using electron-rich and electron-poor salicylic acids as effective pre-cursors for a palladium catalysed *meta*-arylation of phenols (Scheme 31).[65] Their earlier work on *meta*-selective arylation of phenols suffered from harsh reaction conditions (25 atm. of CO_2, high temperature of 190°C). Also electron-deficient phenols were less reactive towards carboxylation and hence were not suitable as effective substrates. However, this new strategy that uses salicylic acids as starting materials allowed *meta*-arylation of phenols with moderately electron-rich or electron poor substituents at the 2- and 4-position. Owing to the ready availability of salicylic acids as well as its easy synthesis from phenols through numerous synthetic pathways[66, 67], this strategy seemed promising. In this paper, Larossa showcased *meta*-arylation of phenols by using a commercially cheap NMe_4Cl reagent as a replacement for silver salts. Further, functional diversifications of these *meta*-arylated products yielded *o*-arylated and *o*-alkylated moieties that are common in natural products and pharma-based molecules.



Scheme 31: Palladium catalysed tandem arylation-protodecarboxylation for *meta*-arylation under palladium catalysis.

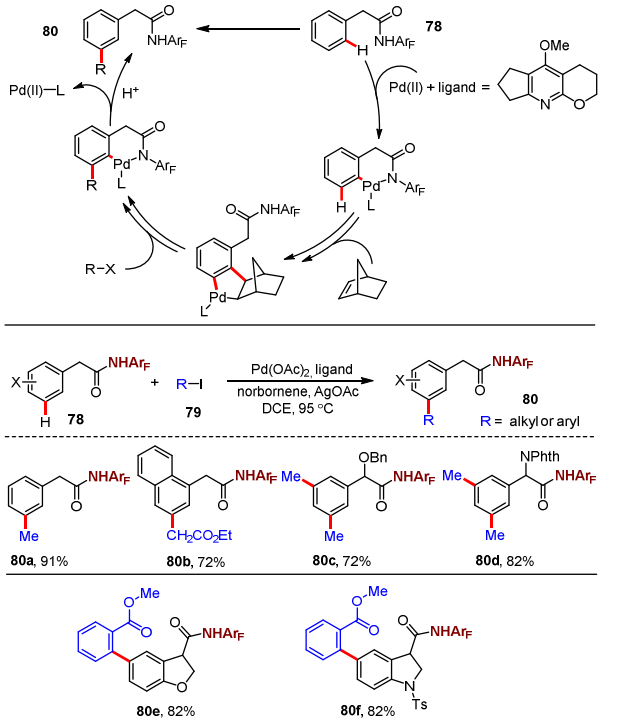
Additionally, *meta*-selective arylation was reported with salicaldehydes as the starting material (Scheme 32).[68] This allowed synthesis of biaryls by using CHO as a traceless directing group which is easy to install, can facilitate *ortho*-functionalization and is readily cleavable. Few examples of the synthetic utility of aldehydes under palladium catalysed conditions exist, *e.g.,* Maiti had previously reported palladium catalysed decarbonylation of aldehydes[69]. A closer look into the transformation revealed the transformation to proceed through a domino oxidation/arylation/proto-decarboxylation route. The silver salt (Ag_2CO_3) used in the reaction helped in the oxidation of salicaldehyde to salicylic acid.



Scheme 32: Palladium catalysed *meta*-arylation using salicaldehydes as starting pre-cursor

2.5 Arylation and alkylation by use of a norbornene mediator

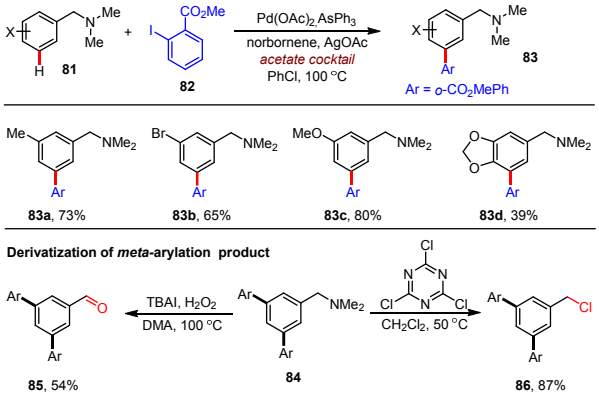
The distinctive reactivity of norbornene in palladium catalysed functionalisation has been unveiled back in 1997 by Catellani and co-workers[70]. Synthesis of 1,2,3-tri-substituted arenes containing aryliodides, alkyliodides and olefins as the buiding blocks had been demonstrated by the reaction. This was based on the differential reactivity of palladium(0), palladium(II) and palladium(IV) species around the catalytic cycle. In March 2015, Yu and coworkers adopted the ubiquity of norbornene as an effective mediator in performing a catalytic *meta*-C–H activation using *ortho*-directing groups (Scheme 33) .[71] Catalysed by palladium acetate and using a pyridine based ligand, phenylacetic acid derivatives were selectively alkylated at the *meta*- position using a *N*-2,3,5,6-tetrafluro-4-trifluromethylphenylamide based directing group with either methyl iodide, ethyliodoacetate or different organohalide coupling partners. Importantly, applicability of this reaction was shown by performing *meta*-functionalization of biologically significant moeities like mandelic acid and phenylglycine.



Scheme 33: Palladium catalysed norbornene mediated *meta*-arylation.

The same strategy was taken a bit further by performing *meta*-selective arylation with aryliodides. Notably, *meta*-arylation of dihydrobenzofuran and indoline based substrates with methyl-2-iodobenzoates could be useful in terms of late-stage heterocycle diversification (Scheme 33).

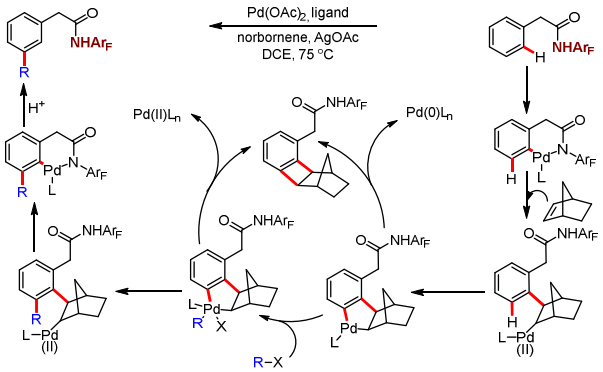
Within a short period of one month, *meta*-selective arylation was independently reported by Dong group by using similar palladium/norbornene catalysis with $AsPh_3$ as the ligand source and chlorobenzene as the solvent (Scheme 34).[72] This work consisted of a simple amine directed strategy which was helpful in several ways. The low molecular weight of dimethylamine, ability of the amine group to perform *reversible ortho*-metalation, its bio-active importance coupled with its easy installation are some noteworthy points of interest. As additives, an 'acetate cocktail' comprising of $LiOAc.2H_2O$,$CsOAc$ and $Cu(OAc)_2.H_2O$ (1:3:0.5) in acetic acid was added. This however helped in providing improved



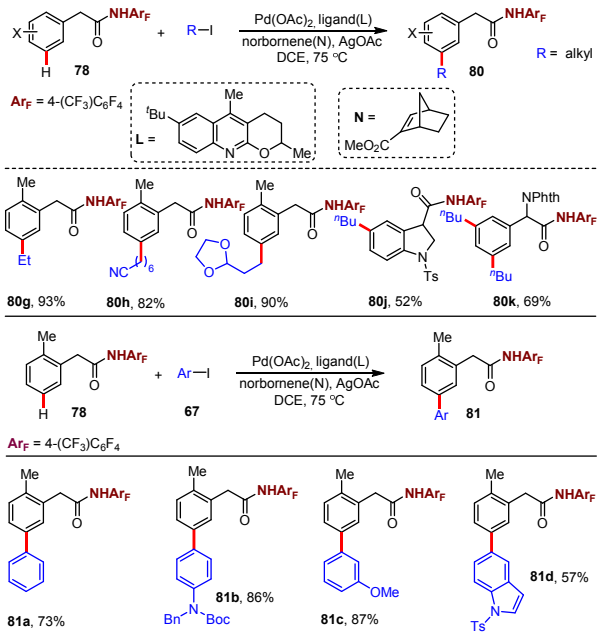
Scheme 34: Palladium catalysed norbornene mediated *meta*-arylation by Dong group.

yields for the reaction rate. Acetic acid helped in speeding up the reaction rate. Substrate scope was demonstrated with different aryl iodides and 2-iodobenzoates. Strongly *ortho*- and *para*- activated 3-methoxy substrates afforded *meta*-arylation in significantly good yields. Arylhalides containing electron withdrawing groups proved to be effective as is observed for typical Catellani arylation reaction. Efficacy of the transformation was further showcased by a post-diversification of the trisubstituted arene derivative to yield synthetically important precursors.

In 2015, Yu group revisited their work on palladium/norbornene catalysed *meta*-C–H alkylation and arylation by intoduction of a 2-carbomethoxynorbornene as a transient mediator.[73] This work overcame the existing limitations of their earlier work. These included an ineffective coupling with *β*-hydrogen containing alkyl partners for alkylation and limited choices of arylcoupling partners (for arylation) since only arenes with *ortho*-coordinating groups could actually undergo successful *meta*-selective coupling. Even Catellani arylation reaction also includes *ortho*-substituted aryl iodides.[74] Use of a 2-carbomethoxy-substituted norbornene in presence of a quinoline based ligand system could also help outwit these limitations by reducing the chances of reductive elimination involved in the catalytic cycle (Scheme 35,36). Subsequently, *meta*-alkylation with butyl iodide derivatives were performed and *meta*-arylation with arenes lacking *ortho*-substituents were also achieved.



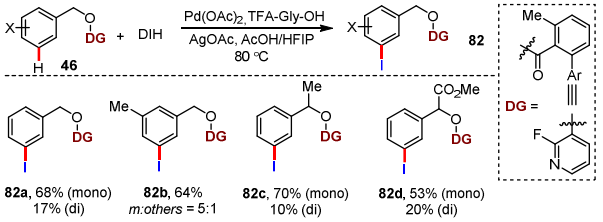
Scheme 35: Palladium catalysed norbornene mediated *meta*-alkylation.



Scheme 36: Palladium catalysed 2-carbomethoxynorbornene mediated *meta*-alkylation with alkylation/arylation.

2.5 Iodination

A serious problem has been the limited functionalization scope with the templates containing weakly coordinating nitrile group. This is because end-on coordination with the palladium metal was problematic in presence of other coordinating reagents. A probable solution in this regard was through the implementation of strong coordination with an identical end on coordination similar to the nitrile group.



Scheme 37: Palladium catalysed template mediated iodination.

Aryliodides act as viable precursors for several carbon-carbon/carbon-heteroatom bond formation reactions. In other words, they form an important starting motif for some renowned cross-coupling reactions including Heck, Suzuki reactions, etc. Greaney and coworkers[21] reported *meta*-C–H bromination under ruthenium catalysed conditions that proceeded with *ortho*-metallation followed by an aromatic electrophilic substitution. However, directed lithiation/iodination was feasible only at the *ortho*-position so far.[75] With the 2-fluoropyridine containing directing group, *meta*-iodination was performed using DIH (1,3-diiodo-5,5-dimethylhydantoin) as the iodinating agent alongwith $Pd(OAc)_2$ as the catalyst, TFA-Gly-OH as the ligand (Scheme 37). This template utilizes the σ-coordinating ability of pyridine ring to position the palladium metal for facile activation of the *meta*-C–H bond.

3. Conclusion

Over the past few years, contributions by eminent scientists in the field of palladium catalysed highly regioselective C–H functionalization have enriched the field of C–H activation based chemistry. Introduction of widely innovative protocols that include strategically designed templates and traceless directing groups aimed towards enabling *meta*-selective C–H activation has been some eminent achievements in this regard. However, a greater challenge still lies in channelising these protocols towards effectuating variegated levels of functionalization excluding those which have been developed so far. This will entail an intricate insight and diligent exploration into the fascinating mechanistic details of these reactions. This will necessitate better development of reaction conditions, advanced level of template design and a motivation to accomplish new challenges.

Acknowledgements

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Notes and references

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