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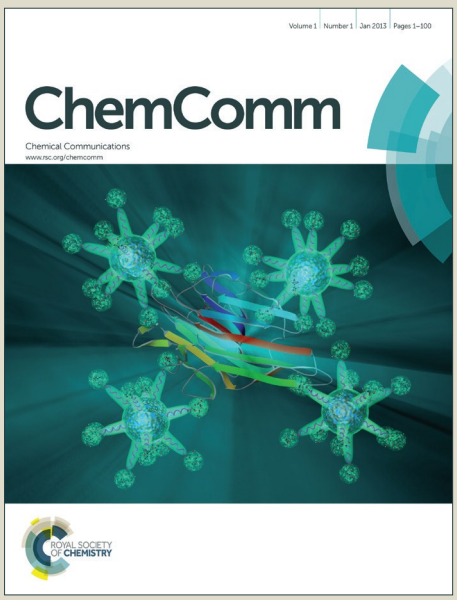

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Feature article

Reaching the south: metal catalyzed transformation of the aromatic *para*-position

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Regioselective functionalization of aromatic arenes has created a rapid insurgence in the modern era of organic chemistry. While the last few years witnessed significant developments on site-selective *ortho*- and *meta*-C–H transformations, there existed very few reports on *para*-C–H functionalization. Recent advancements on template assisted protocols in *para*-C–H activation has emerged as a popular and convenient feat in this area. This review highlights the various protocols developed over the years for selective installation of suitable functional groups at the *para*-position of arenes thereby transforming them into value-added organic cores.

1. Introduction

The alliance between functionalization and selectivity upholds the confederacy of organic chemistry and its applicative privilege in diverse areas of medicinal chemistry, agriculture and material science. Modification of organic cores by installation of functional groups with uncompromised regioselectivity has remoulded routes for synthesis of natural products and complex molecules.[1] Owing to the unequivocal presence of arene systems as core constituents of a vast majority of organic compounds, intense research has been invested in performing highly selective functionalization at the aromatic sp^2 carbon centre. The last three decades recognised an extensive development of reaction protocols facilitating a diverse assortment of functionalization at the *ortho*- position of aromatic arenes. These were mostly guided either by electronic factors or by chelation assisted C–H activation based strategies.[2] Contrary to the innumerable reports on *ortho*- functionalization, advancements in *meta*-C–H functionalization had remained far more elusive in view of the fact that it is a highly electron poor site. This made the *meta*- position quite aversive towards the typical electrophilic substitution reactions. This was until the year of 2012 when the first report on *meta*-C–H functionalization of aromatic arenes using a weak coordination based approach was revealed. With the help of a nitrile containing linker, a highly selective *meta*-C–H olefination reaction was performed by the Yu group.[3] Following this, other different type of functionalization such as acetoxylation, arylation, hydroxylation and iodination was performed at the *meta*- position by Yu as well as by the Tan, Maiti and Li groups using the directing group based approach.[4] Functionalization of C–H bonds therefore circumscribed the *ortho*- as well as the *meta*- position of arenes within its brink. While widening the scope of *meta*-functionalization remained problematic, a selective activation of the arene C–H bond at the *para*-position by directing group approach remained unexplored and was found to be extremely challenging.

Being sites of greater electron density, both the *ortho*- and the *para*-positions of aromatic arenes remain highly vulnerable towards electrophiles. Classical electrophilic substitution reactions are therefore almost equally predominant at these positions resulting in the formation of regioisomeric mixtures. An effective control over the regioselectivity was thus difficult in most of these cases since these were governed by electronic factors and most importantly by steric demands. The foremost choice for the electrophile will be the *ortho*-position but presence of sterically incumbent groups would push the approaching electrophile towards the next electronically activated position in the arene ring, namely the *para*- position. While several advancements made in synthetic chemistry till date patronized unmatched selectivity at the *ortho*- position, few reports existed on a preferential functionalization at the *para*- position. These relied on utilisation of steric and electronic control to favour functionalization at the *para*- position and hence suffered from serious limitation in substrate scopes and poor selectivity ratios, as shall be discussed in this review. Intrigued by this challenge, in 2015, Maiti presented the first ever report on use of a novel template based strategy in performing a highly selective functionalization at the *para*- position of aromatic arenes.[5] This strategy which relies on C–H activation based protocol overcame the long-standing challenge of reaching out to the farthest tip of the aromatic core by use of a transient and easily detachable directing group that would selectively functionalize the *para*- position. Importance of *para*- functionalization can be realised owing to the significance of complex *para*-functionalized molecules in the field of pharmaceuticals, optoelectronics and polymer industry. This review is focussed on the significant developments of *para*-functionalization over the last few years in a chronological order. The major objective lies in creating awareness among the scientific fraternity about the existing aspects of *para*-C–H functionalization and to encourage contributions in order to transform this newly developed area into a significant beneficiary for the scientific world and the allied areas of interest.

2. Diversity of the protocols

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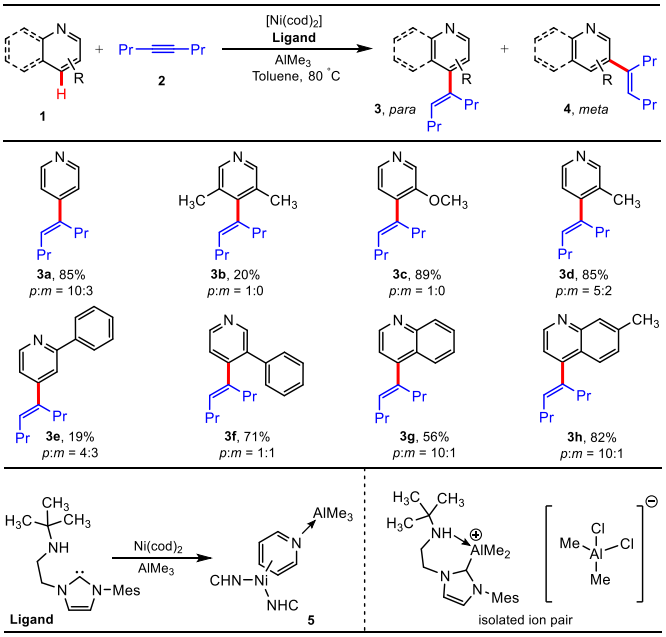
Investigations regarding the attainment of a regioselective *para*-functionalization entailed an intelligent purvey of scientific experiments. Application of a variety of techniques involving functionalization by metal-complex formation, transition metal catalysis and, by far the latest being, use of template assisted C–H activation were implemented by various research groups in the last decade for transforming the *para*- position. *Para*-selective functionalization of arenes has also been performed under metal free oxidative nucleophilic hypervalent iodine(III)-mediated reaction conditions.[6] However, this remains beyond the scope of this review. Herein, we shall discuss the important aspects of such transformations and delineate the gradual evolution of the methodological approaches. Moreover, this review highlights the importance of directing groups as the preferred protocols in assuring selective *para*-C–H functionalization.

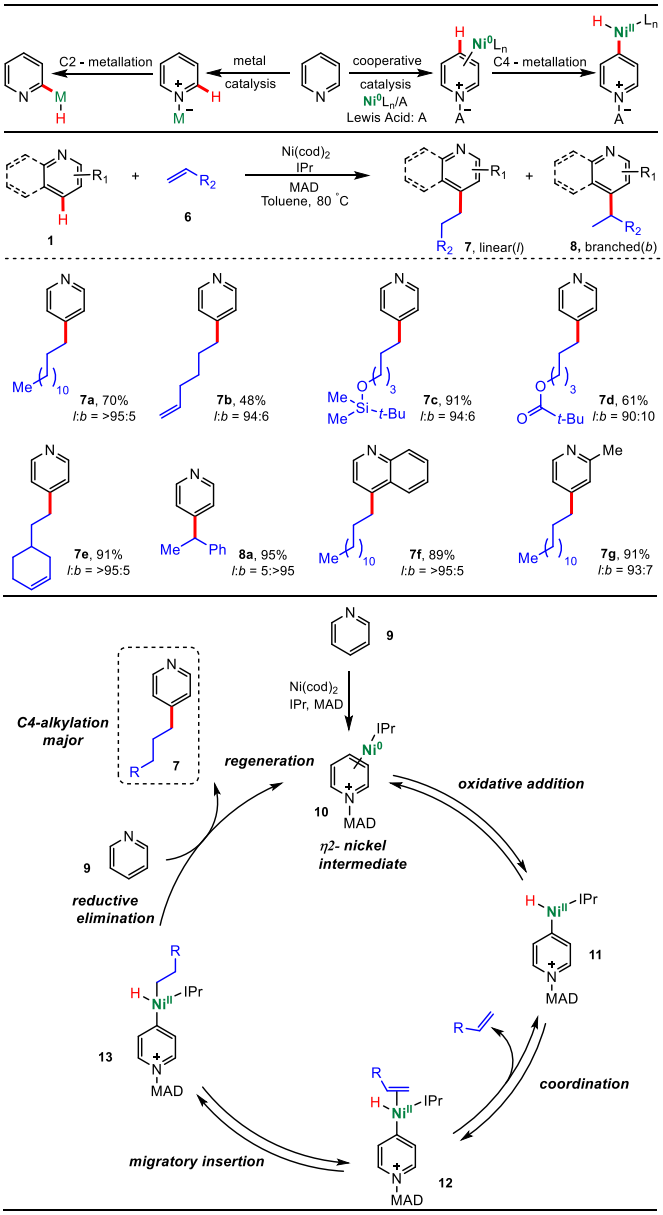
1. By bimetallic / steric-driven bulky metal catalyst:

Combination of bifunctional catalyst and a Lewis acid in functionalization of heterocyclic C–H bonds has been proposed by Hiyama.[7] However, a definite rationale was lacking to support this proposition. In the year of 2010, Ong and co-workers reported the application of an amino-linked *N*-heterocyclic carbenes in conjugation with a nickel-aluminium bimetallic catalyst for selective activation of the *para*-C–H bond of pyridine and quinoline (Scheme 1).[8] This report served as a benign complementary method to the trending use of directing groups facilitating *ortho*- activation at that time. With 2 equivalents of the alkyne, 20 mol% of the $AlMe_3$-amino-NHC, 10 mol% of $Ni(cod)_2$ at 80 °C, a selective *para*-alkenylation of pyridine was carried out with a selectivity ratio of 10:3 (*para*:*meta*). No formation of *ortho*- alkenylated product was observed. Further, Ong reported a structurally characterised three-coordinate nickel(0) complex (**5**, Scheme 1) formed *in situ* in the reaction medium σ-bonded to two amino-NHCs with $AlMe_3$ bridging the nickel complex with the pyridine nitrogen. This bridge was essential in favouring *para*/*meta*- selectivity over that of *ortho*. Deeper introspections into the reaction mechanism was conducted. Isolation of stable ion-pair from C–H catalysis was performed which indicated a decrease in the formation of the Ni–NHC or aluminium-pyridine species with increase in the strength of Al–NHC binding. This was verified by an inverse variation in the Al electrophilicity and reaction yield performed by change in the Lewis acid. A higher degree of π-backdonation from metal to the pyridine moiety was observed which was in accordance with the lower value of primary KIE of 1.25 suggesting C–H bond breakage to be not a part of the rate determining step. Excellent levels of *para*-alkenylation was observed with both pyridine and quinoline derivatives. However, increase in the steric congestion resulted in poor yields (*e.g.* 3, 5- lutidine). Moreover, presence of electron-withdrawing phenyl ring lead to increase of *meta*- activation. Importantly, C–H functionalization in phenyl containing pyridine/quinoline occurred exclusively on the heterocyclic ring in contrast to the contemporary reports.



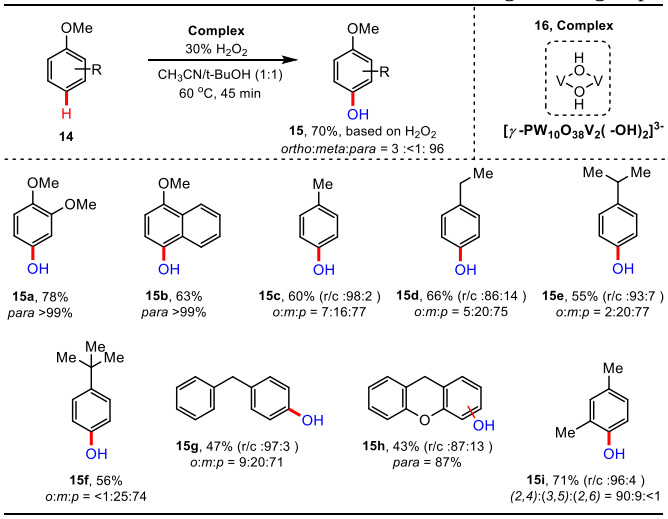
Scheme 1: *Para*-alkenylation of pyridine facilitated by Ni(0)-Al(III) bimetallic catalysis.

In the same year, Hiyama reported a selective C4-alkylation of pyridine by a cooperative nickel /Lewis acid catalysis (Scheme 2).[9] C4-Alkylation and alkenylation was facilitated in the presence of bulky NHC ligands. In presence of 5 mol% of $Ni(cod)_2$, 5 mol% of IPr (1,3-(2,6- diisopropylphenyl)imidazol-2-ylidene) and 20 mol% of $AlMe_3$ at 130 °C, a selective *para*-alkylation of pyridine was carried out with 1-tridecene in 70% total yield (isolated). Regioselectivity was further improved in conjunction with MAD ((2,6-*tert*-Bu_2-4-Me-$C_6H_2O)_2AlMe$) as the Lewis acid catalyst. A small amount of branched alkylation was also obtained. Aliphatic 1-alkenes containing protected alcohols, terminal or internal double bonds as well as vinyl silanes served as good coupling partners for *para*-alkylation. Notably, coupling with styrene proceeded in the presence of IMes (1,3-(2,4,6-trimethylphenyl)imidazol-2-ylidene). In this case, C4-alkylation was obtained by a migratory insertion unlike in the case of aliphatic alkenes *via* a stable benzylic nickel intermediate. Pyridine derivatives such as 2-picoline and quinoline also underwent successful C4-alkylation.



Scheme 2: *Para*-alkylation of pyridine facilitated by cooperative Nickel/Lewis acid catalysis.

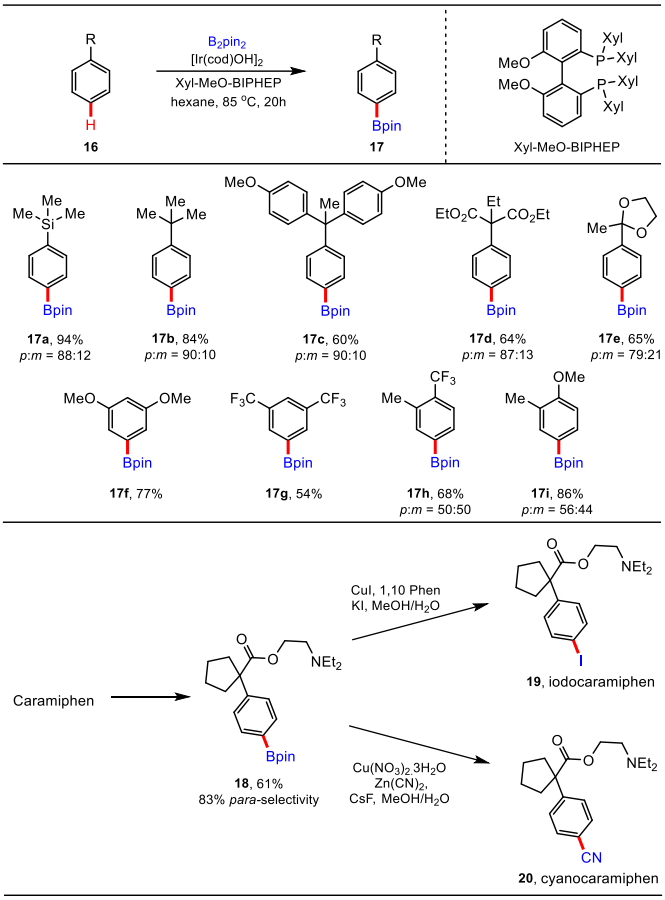
In the year of 2012, polyoxometalate (POM) catalysis was employed in performing a selective functionalization of the *para*-C–H bond. Mizuno and co-workers reported the use of a free-radical, electrophilic, intrinsically recyclable, metal-based oxidant to perform a highly chemo- and regioselective *para*- hydroxylation in a diverse array of arenes.[10] By use of a di-vanadium substituted phosphotungstate [γ-$PW_{10}O_{38}V_2(\mu\text{-}OH)_2]^{3-}$ as a synthetic catalyst based system,[11] formation of *para*-phenols from monosubstituted arenes was carried out (Scheme 3). Moreover, this system displayed extraordinary chemoselective hydroxylation of alkylarenes containing reactive secondary and tertiary alkyl C–H bonds in their side chains. Hydroxylation of anisole with substrate/H_2O_2 ratio of 10:1 in CH_3CN/*t*-BuOH (1:1, v/v) was observed with a selectivity ratio of 3:<1:96 (*ortho*-/*meta*-/*para*-) which is much higher when compared to other stoichiometric reagents such as peroxytrifluoroacetic acid,[12] hydroxyl radical[13] or any other existing H_2O_2 based catalytic systems.[14] Notably, hydroxylation proceeded at 25 °C and also in the presence of air without affecting the performance of the catalyst. Compared to other phosphotungstates that contained a V–O–W and V=O site, reactivity of **16** could be attributed to the presence of the bis-μ-hydroxo site of [OV-(μ-OH)$_2$-VO]. Reducing the catalyst loading to 0.16 mol% resulted in an yield of 67% based on H_2O_2, a turnover number (TON) of 405 and turnover frequency (TOF) of 540 h^{-1}. The latter values were found to be much larger than those found to be for H_2O_2 based catalytic systems. In contrast to the organometallic complexes without bulky ligands and stoichiometric oxidants which led to a mixture of *ortho*- and *para*- substituted phenols,[12-15] regioselective *para*- phenol formation was observed. This could be ascertained to the steric demands created by the POM framework and the substituents that forbid *ortho*-hydroxylation. Various alkylarenes were chemoselectively hydroxylated in the arene cores without any side-chain oxygenation. An unexpected ring:chain ratio for an H_2O_2 based catalytic system of 86:14 for the oxidation of **15d** was obtained. This study highlighted the first chemo-regioselective hydroxylation of **15e, 15g** and **15h** including xanthenes. Intramolecular k_H/k_D ratio was found to be 1.0 which reveals that C–H bond cleavage was not the rate-determining step of the reaction. However, this protocol suffered from certain limitations. Electronic effects of the substituents on the aromatic ring governed the reactivity rates of the substrates. Presence of electron donating substituents resulted in increased yields for the *para*-phenol products than those which contained electron-withdrawing groups.



Scheme 3: *Para*-hydroxylation of aromatic arenes by POM catalyst.

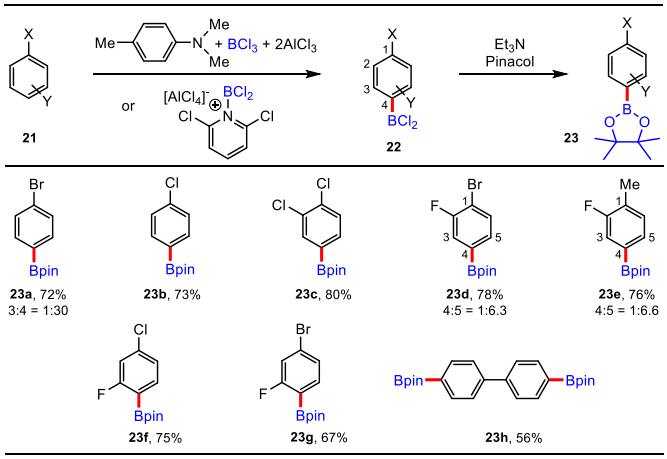
Within a span of three years, Itami and co-workers revealed the use of bulky iridium based catalyst system to allow a steric-driven *para*-C–H functionalization in monosubstituted arenes. In 2015, Itami reported a new generation catalyst that can effectuate *para*-C–H borylation by a steric controlled approach (Scheme 4).[16] After a thorough optimization of the ligand and solvents, a combination of [Ir(cod)OH]$_2$/Xyl-MeO-BIPHEP in *n*-hexane provided 88% *para*-selective borylation with an isolated yield of 94%. Presence of the bulky phosphine ligands on the square pyramidal iridium complex allow a preferential reactivity at the *para*-position of the arene relative to the *meta*- position. This study helped in breaking the stereotyped notion of iridium catalysts' inability to distinguish between *meta*- and *para*-C–H bonds of benzene derivatives. Substrate scope reveals excellent levels of functional group tolerance. However, borylation yields of *meta*-disubstituted benzenes dropped with increase in the steric bulk. Role of the bulky ligand was realized when **17h** and **17i** yielded equal amounts of *para*-products irrespective of the nature of the substituents. Also, bulky substrate such as 1,3-di-*tert*-butylbenzene did not undergo the reaction. Caramiphen is known as an anticholinergic drug effective for Parkinson's disease. Owing to the improved functional property that can be obtained upon *para*-functionalization of benzene core, a *para*-C–H borylation was

conducted on caramiphen to yield **18** in 61% isolated yield. Late stage transformation of **18** helped in formation of **19** and **20** which otherwise required multiple synthetic steps in their preparation.[17]



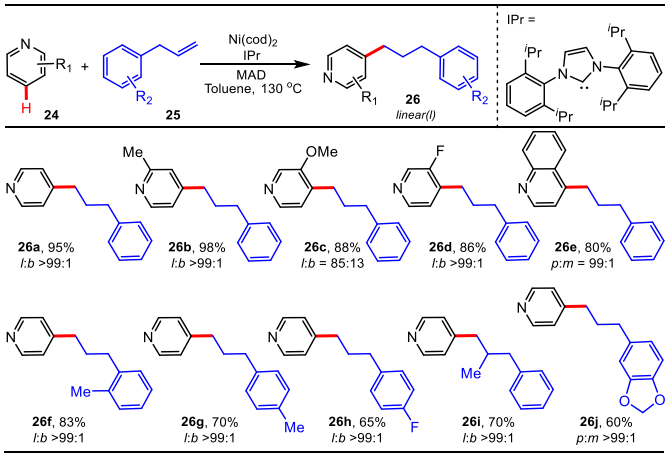
Scheme 4: *Para*-borylation of aromatic arenes by bulky iridium based catalyst system.

In the same year, Ingleson reported electrophilic borylation of haloarenes with a preferred *para*- regioselectivity.[18] Despite significant advances in direct C–H borylation reactions, the scope of borylation was confined to the more nucleophilic arenes. A direct borylation of mono-halobenzenes by electronic control will yield only *para*-borylated arenes. Ingleson reported the electrophilic borylation of deactivated arenes that proceeded with a favourable *para*-selectivity. With a combination of *ortho*-dichlorobenzene and $AlCl_3$ (1:1), or DMTol-BCl_3 (DMTol = *N*,*N*-dimethyl-*p*-toluidine) and $AlCl_3$ (1:2) at 140ºC, *para*-borylation was obtained in good yield (Scheme 5). Following this, *para*-borylation of bromobenzene was performed with DMTol-BCl_3 and $AlCl_3$ in the ratio of 1:2 at 140 ºC in 2 hours with a selectivity ratio of 1:8 (*meta:para*). Use of other combinations like Et_3N-BCl_3 or 2,6-lutidine-BCl_3 with $AlCl_3$ lead to decreased selectivity and formation of benzene as side product. This could be due to the probable disproportionation of bromobenzene in presence of $AlCl_3$. Improvement in the selectivity ratio (*meta*:*para* =1:23) was obtained by lowering the reaction temperature to 100 ºC. Highly regioselective *para*-borylation was obtained for fluoro/chloro-benzenes as well as for 1,3 di-halobenzenes. Use of an equimolar mixture of the crystalline reagent $[(Cl_2Py)BCl_2][AlCl_4]$ and $AlCl_3$ led to an enhanced regioselectivity compared to the former combination. This is because a less nucleophilic amine would mean a higher regioselectivity for the electrophilic borylation. Notably, diborylation of biphenyl at the 4 and 4' position was performed with a 56% isolated yield.



Scheme 5: Electrophilic *para*-borylation of aromatic arenes

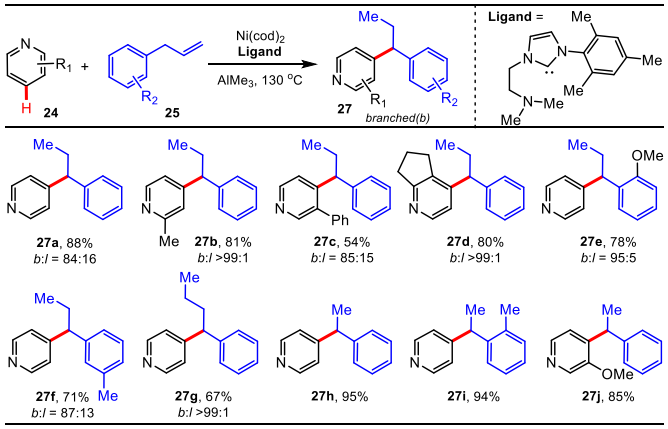
In the same year, Ong revisited their bimetallic Ni/Al catalysis to perform a regio-switchable *para*-C–H alkylation of pyridine with allylbenzene.[19]With 10 mol% of $Ni(cod)_2$, IPr (2,6-diisopropylphenyl)imidazol-2-ylidene) ligand and MAD (methylaluminumbis(2,6-di-*tert*-butyl-4-methylphenoxide)) additive, linear heteroarylation isomer at the *para*- position was obtained with 2 equiv of allylbenzene (Scheme 6). A variety of pyridine and allylbenzene derivatives were surveyed which underwent linear *para*-C–H functionalization with excellent yields and selectivity. Interestingly, quinoline provided *para*-functionalized product with good yield and regioselectivity. Geminal disubstituted allylbenzenes provided uncompromised linear *para*- products.



Scheme 6: Linear *para*-alkylation of pyridine derivatives using allylbenzenes.

Isomerization of the allylbenzene to thermodynamically more stable *β*-methylstyrene would lead to formation of branched products. This could be affected by facilitating the π-coordination of allylbenzene to the metal centre by reducing the steric congestion around the metal. Consequently, branched product was obtained in 88% yield by a change of the ligand and increased amount of $AlMe_3$ (Scheme 7). Substrate scope with an array of pyridine and allylbenzene was performed for this *para*- and branched products. Pyridines with fused 5-membered ring as well as tetrahydroquinoline served to be effective substrates. Viability of the reaction was tested with styrene derivatives along with a non-conjugated olefin containing an sp^3 carbon centre to obtain **27g** as the branched *para*-functionalized product. Absence of hydroheteroarylation at the *ortho*-

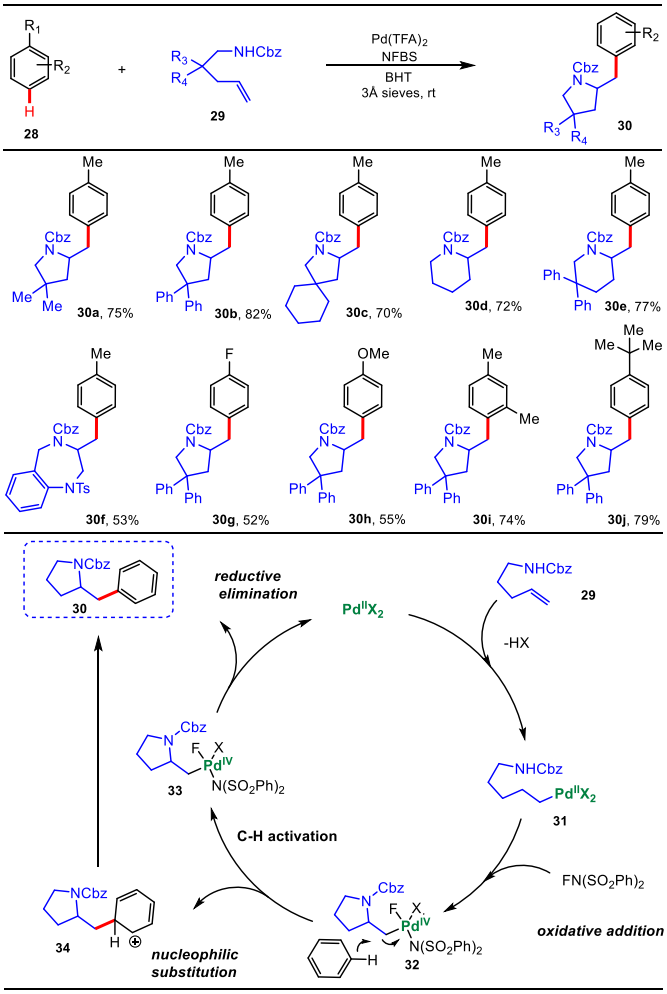
/*meta*- position could be attributed to the steric hindrance imposed by the ligand and Lewis acid.



Scheme 7: Branched *para*-alkylation of pyridine derivatives using allylbenzenes and styrenes.

2. Direct functionalization using transition metal catalysis:

Difunctionalization of alkenes has served to be potential strategy for diversification of organic molecules. Several research groups like Hegedus, Tamaru, Wolfe and others have significantly contributed in performing carboamination at alkenes leading to formation of functionalized molecules.[20] Michael and coworkers, henceforth, also devoted their research interest in performing a palladium catalyzed diamination of alkenes. While their research was *en route*, they made an interesting observation. While working with Cbz-protected aminoalkenes and *N*-fluorobenzenesulfonimide (NFBS) in the presence of a Pd catalyst, a unique change in the solvent from EtOAc to toluene resulted in oxidative carboamination of alkenes with *para*-functionalization in toluene.[21] Optimization of this obtained conditions resulted in an yield of 75% at room temperature with $Pd(TFA)_2$ as the catalyst, 3Å molecular sieve and presence of BHT as a radical scavenger (Scheme 8). Substrate scope was performed with a variety of aminoalkenes and arenes. An array of five, six and seven membered nitrogen containing heterocycles could be formed under these conditions. Nucleophilic arenes react preferentially although electron-poor arenes like nitrobenzene, methylbenzoate, etc. did not react under the obtained set of reaction condition. The mechanism for the concerned transformation was proposed to be functional by two possible pathways: either through an electrophilic substitution on the arenes by an intermediate Pd(IV)-alkyl complex or through C–H activation of the arene by the Pd(IV) species followed by reductive elimination.

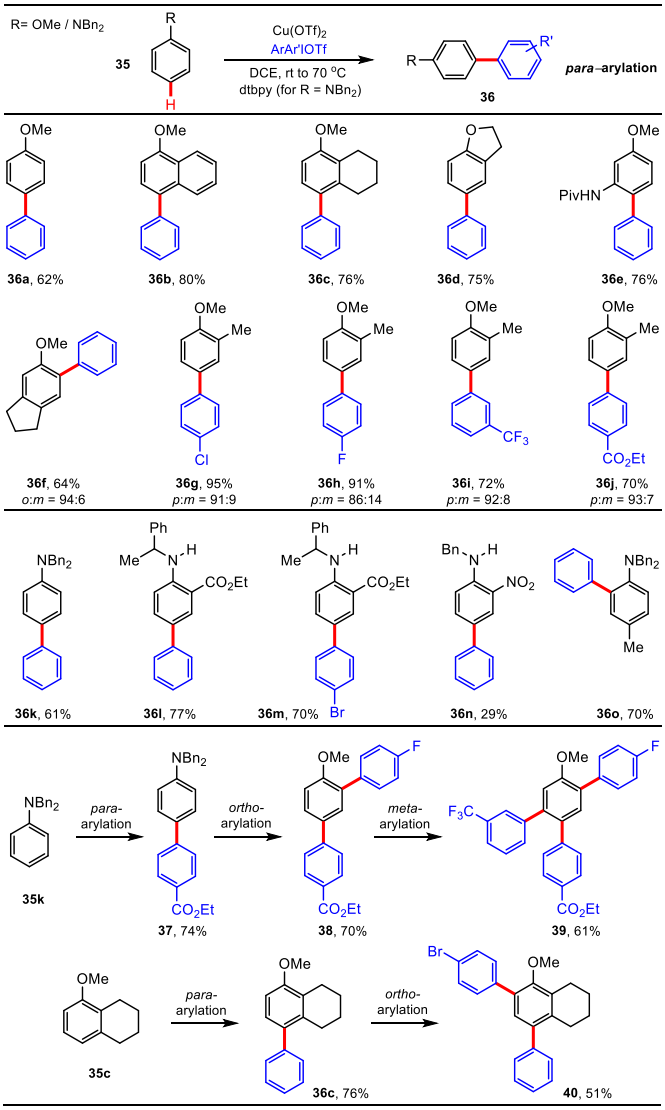


Scheme 8: (A) *Para*-functionalization of toluene derivatives by carboamination of alkenes. (B) Plausible mechanism

The importance of biaryls from synthetic point of view has long been realised. Nevertheless, synthesis of such biaryls required the prior availability of pre-functionalized starting precursors. This indirectly necessitated involvement of a series of a highly regioselective chemical transformation for preparation of these functionalized precursors.

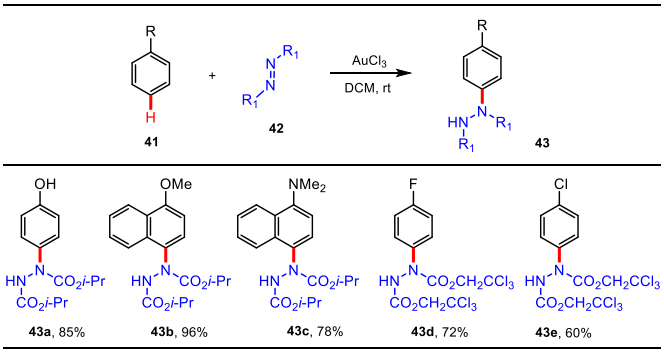
In 2011, Gaunt and co-workers reported a copper catalysed method for *para*- selective arylation in phenols and derivatized anilines (Scheme 9).[22] The reaction proceeded under a mild condition, involved inexpensive catalysts and could tolerate a wide exemplar of functionalities. Using their previously reported reaction conditions for *meta*-selective arylation in pivanilides,[1a] Gaunt performed a highly *para*- selective arylation for anisole with an isolated yield of 62%. A competitive directing ability between methoxy and pivanilide groups resulted in arylation at a position *para*- to OMe group showing its greater electronic influence. Moreover, blocking of the *para*- position resulted in *ortho*- arylation. Hence, the protocol could be mentioned by an alias in parallel with the Friedel Crafts type S_EAr arylation. Both symmetrical and unsymmetrically substituted diaryliodonium salts could be successfully used as the aryl coupling partner. This transformation was further extended to perform *para*-arylation of N,N-dibenzyl aniline at 50 °C. Presence of 2,6-di-*tert*-butylpyridine (dtbpy) as a base helped in capturing the *insitu* generated TfOH. Formation of heterocyclic biaryls was also showcased by this protocol

although presence of electron-withdrawing substituents led to a reduction in the yield of *para*-arylation. Thus, the protocol clearly depended on electronic factors. Upon blocking of the *para*-position, only mono *ortho*-arylation was obtained rather than diarylation. This is because installation of an aromatic ring pushed the nitrogen atom of the aniline out of the ring planarity preventing second arylation. Novelty of this protocol was further highlighted by showcasing the *ortho-/ meta- / para-* and *ortho-/para-* arylation of anilines and phenols respectively. A further insight into the mechanistic details of the protocol was presented. In absence of the catalyst, the reaction proceeded very slowly and under high temperature conditions resulting in lower yields. Progress of the reaction in absence of the catalyst could be explained by the formation of an electrophilic aromatic species generated by a thermal induced dissociation of the counter ion. This species is then attacked by the electron-rich arene. In presence of the catalyst, dissociation of the triflate ion occurs giving rise to an activated aryliodonium species which explains the increase in the reactivity. In this transformation, the substrates displayed selectivity patterns that are congruent with classical nucleophilic reactivity. Unlike the single electron transfer (SET) process that is found to occur for iodonium salts with electron-rich arenes and heteroarenes,[23] formation of aryl radical cation is not plausible as SET would give rise to a regioselective mixture of biaryls products. This was further confirmed by the fact that radical scavengers proved to have no effect in the reaction. Thus this arylation methodology was typical of a copper catalyzed "Friedel-Crafts arylation" reaction.



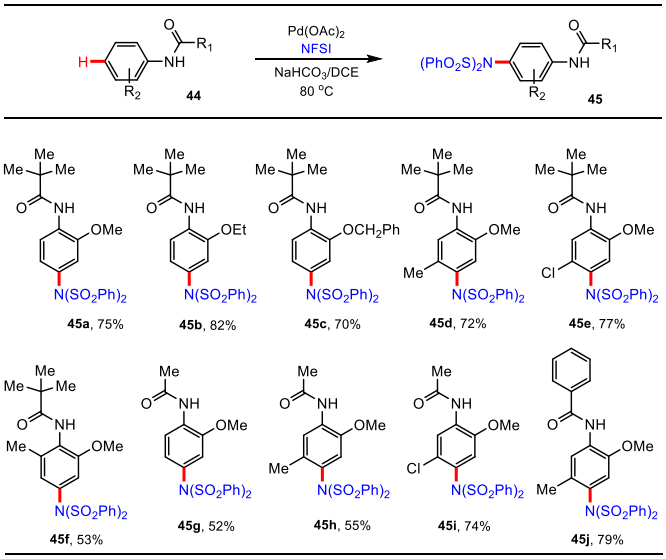
Scheme 9: (A) Copper catalysed *para*-arylation of anisole derivatives. (B) Copper catalysed *para*-arylation of aniline derivatives. (C) Late-stage functionalization of *para*-arylated aniline and anisole derivatives.

In the same year, Y. Zhang and coworkers developed a gold(II) chloride catalyzed direct amination of arenes with azodicarboxylates.[24] The synthetic importance of aryl hydrazides for the preparation of heterocycles such as indoles, pyrazoles, *etc*. further supported the significance of the strategy. $AuCl_3$ has been well known to activate the C(aryl)–H bond of arenes as well as azodicarboxylates. Moreover, the aryl gold(III) complexes could be generated under anhydrous conditions.[25] Zhang investigated the catalytic activity of gold(III) chloride in the direct amination of arenes with azodicarboxylates in presence of DCM solvent and with catalyst loadings as low as 1 to 5 mol%. Interestingly, both electron rich and electron deficient arenes could be aminated under mild conditions (Scheme 10). Mono-substituted arenes were aminated at the *para*-position with respect to the arene substituent with excellent regioselectivity.



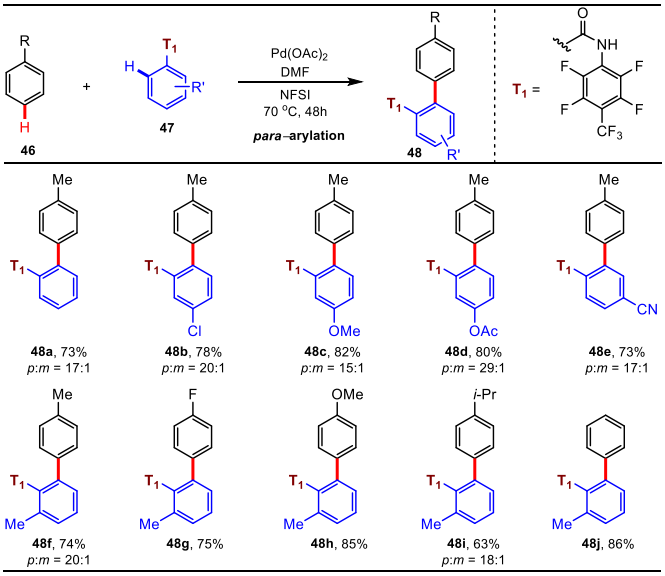
Scheme 10: Gold(III) chloride catalysed *para*-amination of arenes.

Direct formation of aromatic C–N bonds is of wide interest owing to the importance of aromatic amines in a diverse range of fields like agrochemicals, pharmaceuticals, conducting polymers, etc. In 2011, Zhang developed an amide directed palladium catalyzed regioselective *para*- C–N bond formation in aromatic cores (Scheme 11).[26] Inspired by Hartwig's work on palladium catalyzed intramolecular C–H amination by a non-nitrene based nitrogen source,[27] Q. Zhang and co-workers independently developed an intermolecular analogue of this reaction using *N*-fluorobenzenesulfonimide (NFSI) as the nitrogen source. In presence of $Pd(OAc)_2$ as the pre-catalyst and DCE as solvent at 80 °C, *para*-aminated products were formed with substrates like **44a-j** containing an *ortho*-methoxy substitution. A variety of substrates were examined including substrates with two *ortho*-positions blocked. In every case, amination proceeded with high *para*- regioselectivity in presence of the non-nitrene nitrogen source. However, diacetamide substrates or substrates containing electron withdrawing nitro group did not work for this protocol.



Scheme 11: Palladium catalysed *para*-amination of aryl amide derivatives.

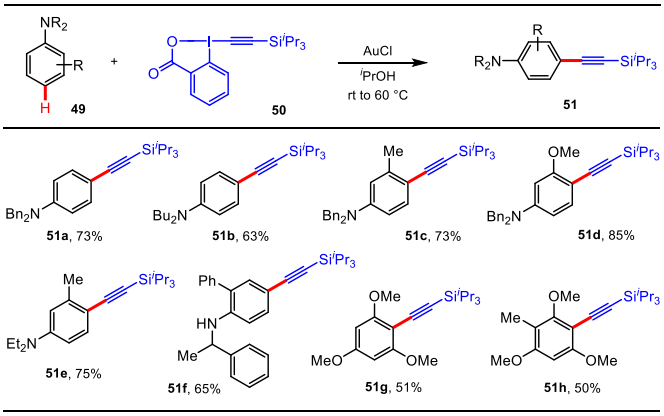
A growing resurgence for a C–H coupling reaction between two aryl partners was prominent. Most often, such a cross-coupling result in the formation of regioisomeric mixtures. Synthetically useful strategies have been developed in this regard by Buchwald and Dong for mono-substituted arenes.[28] In 2011, Yu developed a palladium catalysed C–H / C–H coupling reaction of benzamides with mono-substituted arenes in presence of F^+ as an oxidant (Scheme 12).[29] Arylation proceeded with high *para*-selectivity on a wide range of benzamides containing both electron donating as well as electron-withdrawing groups. A significant *para/meta* ratio of 13:1 with 70% yield was obtained with 1-fluoro-2,4,6-trimethylpyridinium triflate (NFTMPT) as the F^+ source and with DMF as an additive. Further optimization of the oxidant showed NFSI to provide high *para*-selectivity (*para*:*meta*=20:1). Conversion of the amide products into carboxylic acid intermediated paved the way for an easy synthesis of drug molecules such as Losartan and Valsartan. Scope of the arene coupling partners comprised of electron-donating and halogen containing benzenes. Superseding the NFSI source with $Na_2S_2O_8$ led to poor selectivity. This was suggestive of a plausible [ArPd(IV)F] species (confirmed by obtaining 5% *ortho*- fluorinated product) to be essential for the selective *para*-C–H cleavage. Selectivity was also found to diminish on using a triflamide group in place of the carboxylic acid derived from 4-trifluoromethyl-2,3,5,6-tetrafluoroaniline ($ArNH_2$). Thus role of the nature of the amide handle in determining *para*-selectivity was perceivable. In the same year, *para*-arylation of toluene with aryl aldoxime ethers, *N*-methoxybenzamides and anilides were also reported by Cheng and You.[30]



Scheme 12: Palladium catalyzed *para*-arylation of arenes by C–H/C–H coupling reaction with benzamides.

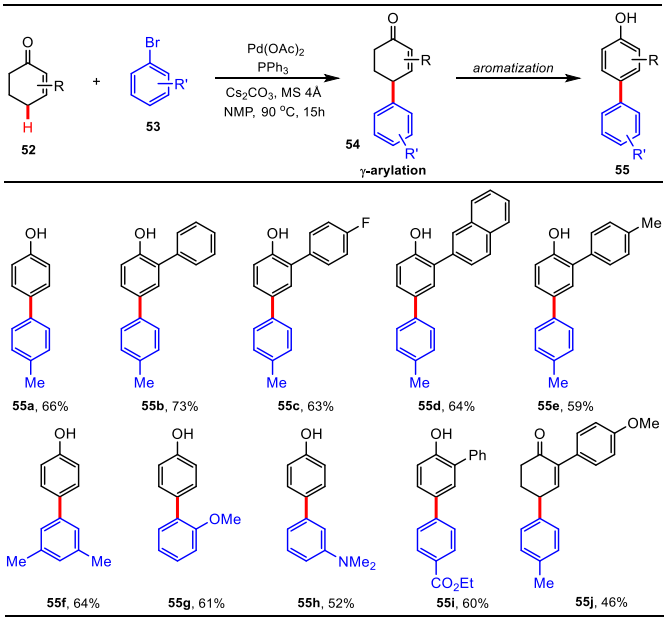
For eons together, Sonogashira reaction has remained as an important tool for establishing sp^2-sp bonds that allowed routes to heteroarylacetylenes.[31] This method, however, suffered from a drawback owing to a required pre-functionalization of the sp^2 carbon. In parallel to several groups[32] who worked towards developing an alternative for the same, Waser group has showcased their research interests towards synthesis of silylated acetylenes whose efficient deprotection allows access to terminal alkynes.[33] In 2012, Waser demonstrated the first example of a *para*-selective gold catalyzed alkynylation of anilines using triisopropylsilylethynyl-1,2-benziodoxol-3(1H)-one (TIPS-EBX, **50**) as an alkynes transfer reagent (Scheme 13). *Para*-alkynyl anilines have proved as important molecules in material science because their chromophoric character renders significant photochromic and photoswitchable properties. Notably, nitrogen containing groups have been known to inhibit gold catalysis in many cases.[34] Owing to their more nucleophilic character relative to carbamates and easy removal of the benzyl groups, *N*,*N*-dibenzylaniline was chosen as model substrate. With 5 mol% of AuCl as the catalyst, 1,4 equivalents of TIPS-EBX and in presence of *i*-PrOH as the solvent, *para*-alkynylated anilines were obtained in 73%

isolated yields at room temperature. Smaller alkyl groups led to formation of complex mixtures in minor amounts which accounts for the strict regioselectivity of the reaction with respect to aromatic electrophilic substitution. In addition to the compatibility of the reaction in presence of methoxy and halogen substituted *meta*-positions, mono-protected anilines were also seen to work well. This demonstrated the tolerance towards free N–H bonds. The reaction was also extended towards successful *para*-alkynylation of trimethoxybenzene derivatives.



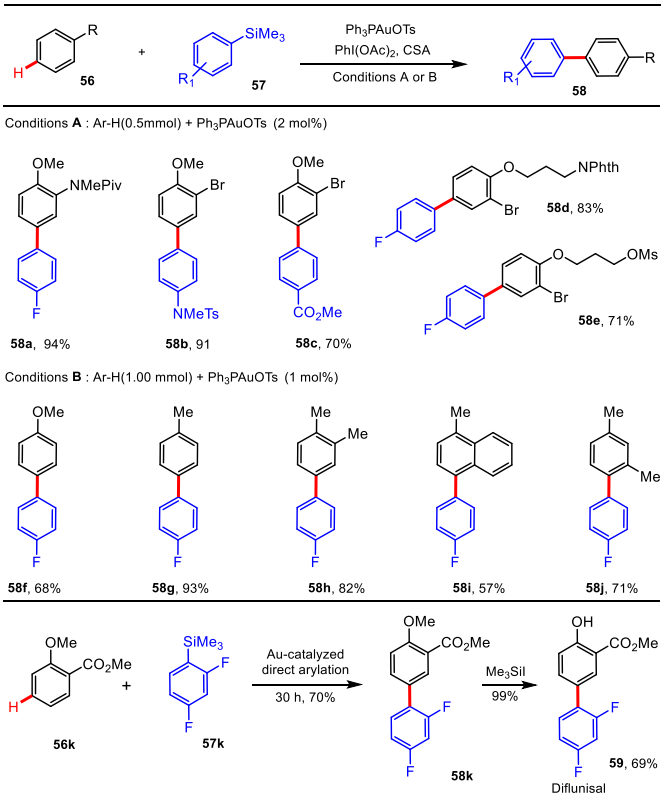
Scheme 13: Gold catalysed *para*-alkynylation of arylamines.

Subsequently, in the same year, Imahori took an alternative approach towards formation of biaryls by *para*-C–H activation. Imahori developed a palladium catalysed tandem *γ*-arylation/aromatization of 2-cyclohexen-1-one derivatives with aryl bromides.[35] Through this approach, formation of *para*-arylated phenols directly from the phenol surrogates in a single step could be conceived. With 20 mol % of $Pd(OAc)_2$ and 40 mol% of PPh_3, an yield of 66% was obtained in NMP at 70 °C (Scheme 14). Substrate scope with both the phenol surrogates and the aryl bromides were investigated. Position of the substituents on the aryl halide did not affect the reaction. A detailed study revealed the requirement of an excess aryl bromide for promoting aromatization. Moreover, homo-coupled products were also found to be generated during the aromatization process. Detection of an intermediate **54** was evidential for the proposed *γ*-arylation/aromatization process.



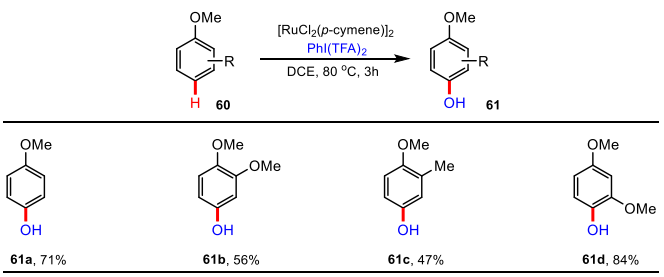
Scheme 14: Palladium catalyzed *para*-arylation by tandem *γ*-arylation/aromatization of 2-cyclohexen-1-one derivatives with aryl bromides.

Gold catalyzed reactions of arylsilanes have been found to attract widespread attention owing to their mild conditions, low loadings and site selectivity. The offered complementarity and orthogonality of these reactions were exploited by Lloyd-Jones and Russell in putting together the iodine(III) mediated homocoupling reactions of Ar–H and oxidative gold catalyzed homocoupling of $ArSiMe_3$, both of which operate through the traditional electrophilic aromatic substitution reaction pathways.[36] They envisaged a site-selective gold-catalyzed oxidative heterocoupling reaction of arylsilanes with arenes thereby furnishing a step-economic construction of complex biaryls. In presence of $Ph_3PAuOTs$ as the precatalyst with low loadings of 1-2 mol%, an active oxidant formed *in situ* from $PhI(OAc)_2$ and camphorsulfonic acid along with $CHCl_3/CH_3OH$(50:1) as the solvent, arylsilanes were made to react with simple arenes yielding *para*-arylated products with excellent selectivity and good yields at temperatures ranging from room temperature to 65 °C (Scheme 15). Reaction conditions were varied depending upon the electronic nature of the substrates. Both electron-rich and electron-deficient substrates worked well under the reaction conditions. Site of arylation was independent of the presence of the pre-installed functionalities. The selectivity for electron rich aromatics was complementary to the deprotonation-type arylation mechanisms which favour electron-poor substrates or *ortho*-directing groups. Notably, the reaction condition favoured heterocoupling over homocoupled products, tolerated a wide range of functionalities and provided economic and efficient catalysis at room temperature. Easily synthesizable silyl starting precursors allowed non-toxic conditions and lacked the air sensitivity displayed by organometallic reagents traditionally used in similar classical cross-coupling reactions. Efficacy of the protocol was further demonstrated by the synthesis of non-steroidal anti-inflammatory drug like diflusinal.



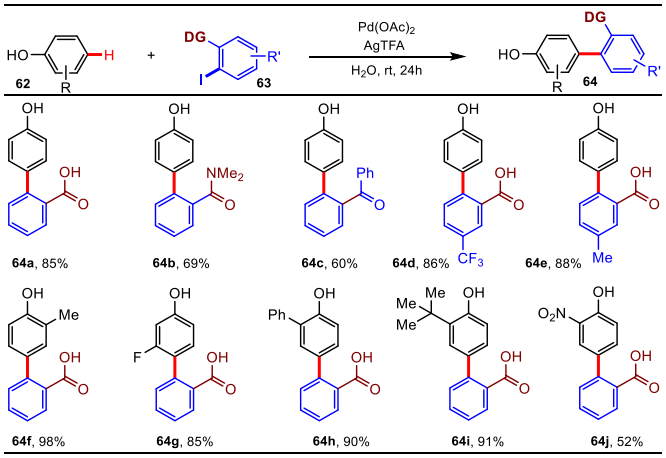
Scheme 15: (A) Gold catalysed *para*-arylation by arylsilanes. (B) Synthesis of anti-inflammatory diflusinal drug.

In parallel to the transformations involving palladium catalysed C–O bond formation, reactions with ruthenium(II) as the catalysts were also reported. In 2013, Ackermann and co-workers reported the first example of a ruthenium catalysed *para*-hydroxylation of aryl carbamates (Scheme 16).[37] Despite the ubiquity of phenols in a broad utilitarian spectrum, a ruthenium(II) catalysed direct C–H bond oxygenation of phenol had remained unknown. The established protocol was applicable to a wide array of substrates without Lewis basic directing groups. With $[RuCl_2(p\text{-cymene})]_2$ as the catalyst, $PhI(TFA)_2$ as the oxidant and DCE as the solvent, a variety of anisole derivatives were selectively hydroxylated at the *para*-position with respect to the OMe group. However, the reaction suffered severely from limited range of substrate scopes. On addition of catalytic (10 mol%) or stoichiometric (1 equiv) amount of TEMPO to the reaction medium lead to reduction in the yield (43% and 5% respectively). This can be justified as per a single-electron transfer oxidation to be operative in the above transformation.



Scheme 16: Ruthenium catalyzed *para*-hydroxylation of arenes.

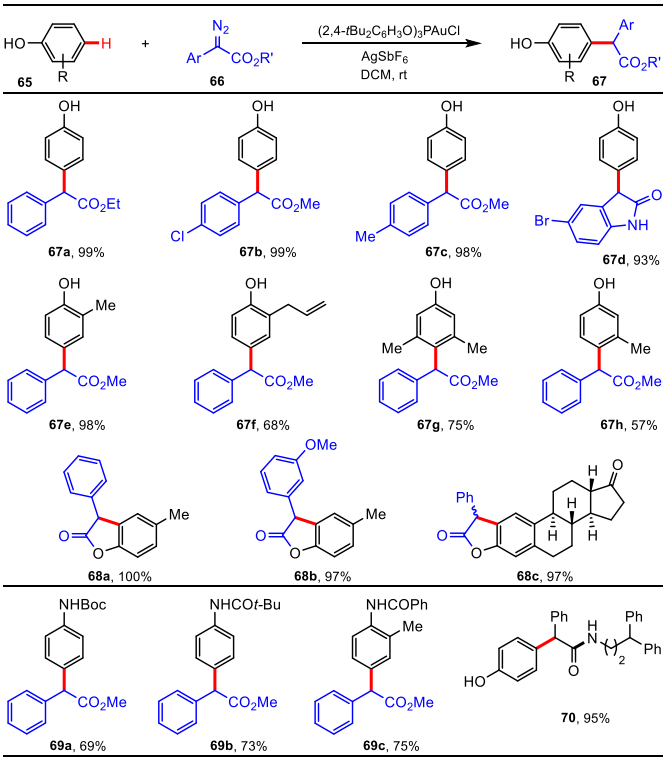
Following this, in 2013, Zhou and co-workers explored a highly *para*-selective arylation of phenol using 'water' as a green solvent.[38] Direct arylation strategies usually required harsh reaction conditions, a surplus of the arene coupling partner and were limited by problems of regioselectivity. Importance of a chelator allowing the synthesis of *ortho*-functionalized biaryls through late-stage modification has been realised. Zhou reported a novel stratagem for a palladium-catalyzed *para*-arylation of unprotected phenols with *ortho*-substituted aryl iodides (Scheme 17). The reaction uses inexpensive, environmentally friendly and non-toxic water as the solvent under extremely mild reaction conditions. With $Pd(OAc)_2$ (5 mol%)/AgTFA as the catalyst combination in water, an isolated yield of 85% was observed for *para*-arylated phenols. Presence of an *ortho*-coordination group helped in augmenting the oxidative addition of the transition metal to facilitate a thermodynamically stable intermediate and the activation of the phenolic substrates. This was in stark contrast to the well-known procedures of direct C–H arylations.[39] With a wide array of 2-iodobenzoic acids and aryl iodides with varied classes of *ortho*-substituted directing groups, excellent levels of *para*-selectivity was obtained. In absence of the *ortho*-substituted coordinating groups, no arylation was obtained. A diverse array of phenol substrates were screened to provide *para*-arylated products with uncompromised selectivity. Nevertheless, higher chelating ability in salicylic acid prevented its participation in the concerned transformation. Addition of a catalytic amount of acid was required to improve reactivity in case of the phenols with electronic deficiency. Replacing AgTFA with silver nitrate helped in achieving **64j** through a tandem process which is otherwise difficult to synthesize by simple arylation in 2-nitrophenols. Employment of this aqueous catalytic system for a direct oxidative C–H/ C–H cross-coupling between phenol and the aromatic acid at elevated temperatures (100 °C) resulted in a poor selectivity of 2:1 (*para*:*meta*). Further, scaling-up of the reactant amount allowed gram-scale formation of products.



Scheme 17: Palladium catalyzed *para*-arylation of phenols in aqueous medium.

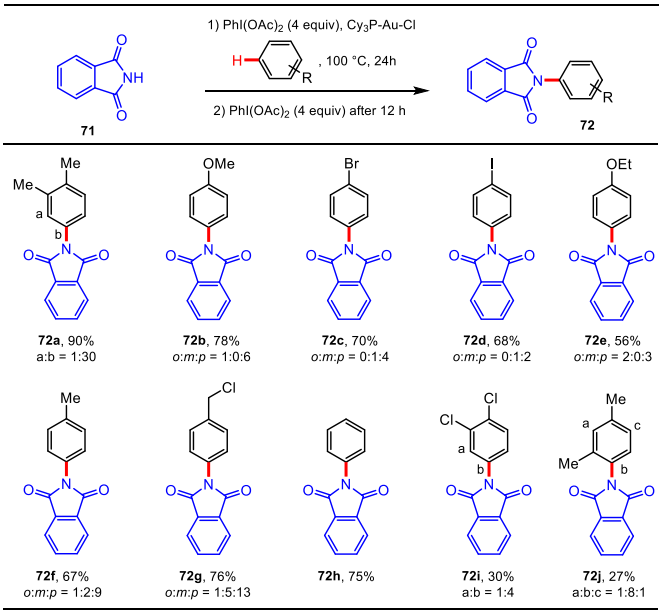
In 2014, Zhang developed an intermolecular gold catalysed site-selective *para*-functionalization of unprotected phenols and N-acylanilines with *α*-aryl *α*-diazoacetates and diazooxindoles (Scheme 18).[40] This was done with an intention to develop a highly selective direct C–H functionalization protocol that would ensure a simple one-step transformation, improved scalability and a mild condition with low catalyst loading. Carbene transfer reactions of diazo compounds mediated by transition metals have been well-explored by eminent scholars like Yu, Peres and others.[41] Owing to the innate carbophilic

π-acidic and catalytic activities of gold complexes, few reports exist on gold-catalyzed carbene transfer methodologies.[42] This strategy provided a simpler pathway for synthesis of diarylacetates overcoming any possibilities for an O–H bond insertion.[43] With Ph_3PAuCl (5 mol%), $AgSbF_6$ (5 mol%) and tris(2,4-di-*tert*-butylphenyl) phosphite as the ligand in presence of dichloromethane at room temperature, a reaction between methyl *α*-phenyl-*α*-diazoacetate and phenol yielded *para*-C–H functionalized product with an isolated yield of almost 99%. Neither any *ortho*- nor *meta*-C–H functionalized product was detectable. Scope of the phenolic substrates as well as of the diazo compounds with both electron donating and electron withdrawing compounds were duly investigated that yielded *para*-functionalized products in moderate to excellent yields. Formation of 3-aryl oxoindoles with a free hydroxyl group could be easily conceived. The catalyst was found to favour *para*-C-H functionalization over cyclopropanation[44] of alkene as was seen with **67f**. Sterically hindered *para*-C–H bond underwent the reaction successfully without giving any O–H insertion product. Presence of methoxy group also yielded some amount of *ortho*-functionalized product along with **67h**, indicating its role as a directing group. A purposive blocking of the *para*-position resulted in *ortho*-functionalization thereby opening an alternative for the preparation of estrone derivatives and 3- aryl benzofuranone, which form important central motifs for several natural products. Extending the protocol to *N*-acyl protected anilines furnished *para*-C–H functionalized products in moderate to good yields without any competitive N–H bond insertions. The acyl protection was also necessary as the basic aniline led to inhibition of the catalyst's reactivity by coordination. Indisposition of the reaction to show any kinetic isotope effect meant that cleavage of the C–H bond is not the rate-determining step. This would imply an electrophilic addition of the gold catalyst followed by a 1,2 hydride migration. Late stage functionalization of the *para*-products yielded molecules of significant scientific interest including Cannabinoid CB1 receptors like **70**.



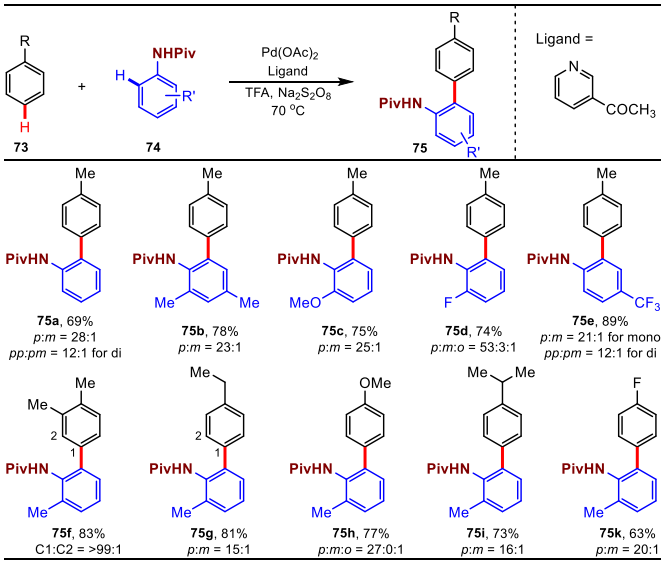
Scheme 18: Gold catalyzed *para*-functionalization of unprotected phenols and *N*-acylanilines.

In the following year of 2015, DeBoef reported a gold catalysed *para*-selective formation of C–N bond.[45] DeBoef designed a strategy to perform an augmented regioselective *para*-amination that would proceed through an electrophilic aromatic metalation (EAM) pathway. The reaction would hence follow metalation of the arene by gold catalyst rather than a non-catalyzed radical mediated amination protocol.[46] In presence of 10 mol% of Cy_3P-Au-Cl, 4 equiv of $PhI(OAc)_2$, phthalimide *N*-protected amines were synthesized at 100 ^oC with excellent *para*- selectivity (Scheme 19). Comparative studies revealed the protocol to facilitate amination for electron-rich aromatic systems relative to electron-deficient ones thereby supporting a likely EAM cycle. The predominant *para*- selectivity was attributed to the larger size of the gold atom that prevents a competitive *ortho*-C–H functionalization. A competing metal-free, radical-mediated reaction pathway yielded minor amounts of *meta*-substituted products in less-electron rich systems unlike in chlorobenzene which underwent an exclusive *para*- amination. Presence of the oxidant ensured a suppression of the biaryl side product formation. Mechanistic studies provided a KIE value of 1.04 which was inconsistent with a gold-mediated concerted metalation-demetalation (CMD) based C–H activation protocol and that an EAM pathway based on an Au(I)/Au(III) catalytic cycle was operative. Owing to the easy conversion of phthalimides into free amines, a promising strategy for regioselective formation of aniline derivatives was therefore realized.



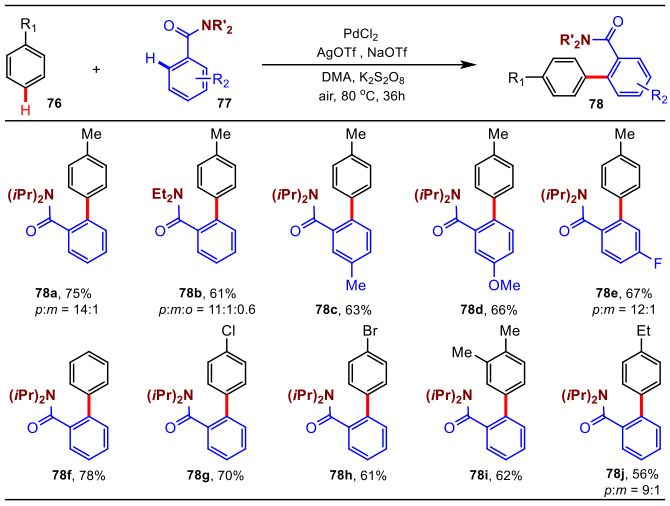
Scheme 19: Gold catalyzed *para*-amination of arenes.

In the same year, Yu group revisited their previous report[29] on the requirement of a stoichiometric amount of F^+ as a bystanding oxidant to maintain *para*-regioselectivity.[47] This time they presented the use of a catalytic pyridine based ligand that yields regioselective *para*-functionalization of monosubstituted arenes by a double C–H activation step without the requirement of any F^+ reagent. It was aimed at replacing the fluoride at the Pd(IV) centre by the ligand without affecting *para*- selectivity at the C–H bond breaking step. With pivaloyl-protected aniline substrate and toluene, a preliminary screening with pyridine as the ligand, $Pd(OAc)_2$ as the catalyst in presence of $Na_2S_2O_8$ as the oxidant afforded *para*-selectivity in the ratio of 15:1 (*meta*:*para)* (Scheme 20). A diligent screening of a variety of pyridine and quinoline ligands confirmed 3-acetylpyridine and methyl nicotinate as to be the best choice as the ligands. Importance of the ligand nature in determining regioselectivity in non-directed C–H activation was demonstrated. The π-acceptor character of the pyridine ligand enhanced the electrophilic nature of the Pd centres. Presence of electron-withdrawing groups at the *para*- and *meta*-positions of pyridine improved *para*-selectivity. A ratio of *para:meta* of 28:1 was obtained with a 30 mol% of ligand loading. A variety of substituted anilide and arene substrates with both electron-donating and withdrawing groups were tested for this reaction. Biaryl formation in good yields for anilides with electron-withdrawing substituents were obtained by an increase in ligand loading and TFA amount. Following the cyclopalladation at the first C–H activation step, a π-acceptor-ligand-supported Pd(II)/Pd(IV)species was presumed to mediate electrophilic palladation at the second C–H activation step as inferred by the lack of kinetic isotope effect. Sterically incumbent ligand-attached palladium centre helped in a preferential reactivity by an electrophilic palladation route at the *para*-centre.



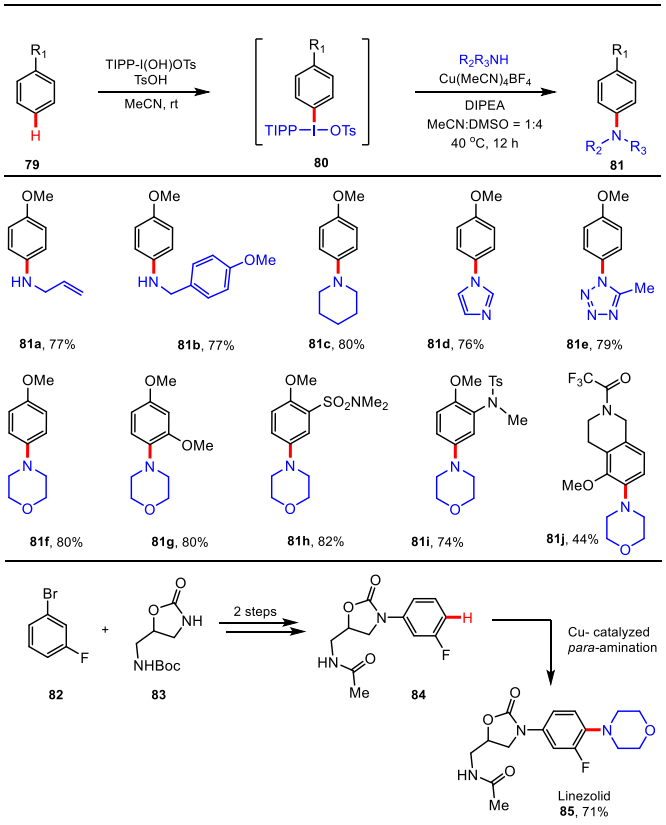
Scheme 20: Palladium catalyzed *para*-arylation of monosubstituted arenes in presence of pyridine based ligand.

Within a period of a month, Guan and co-workers reported *para*-arylation of mono-substituted arenes through oxidative coupling of arenes with tertiary benzamides.[48] Weak coordination by the amide group as well as electron deficiency of the aryl ring prevented reactivity of tertiary benzamides in C–H activation reactions. With $PdCl_2$ as the catalyst (10 mol%), AgOTf (20 mol%), NaOTf (20mol%), DMA (2 equiv) and $K_2S_2O_8$ (2 equiv) at 80 °C, biarylation occurred by coupling between benzamide **77a** and toluene with *para*-regioselectivity in the ratio of 14:1 (*para*:*meta*) (Scheme 21). In absence of the triflate salts or the oxidant $K_2S_2O_8$, selectivity was found to be diminished thereby validating the necessity of the triflate anion as well as the oxidant for improved yield and selectivity. Reaction condition was simple to handle and was stable at air. With this "standard condition", a survey of the scope of benzamides and arenes was carried out. Presence of *ortho*-substituents like methyl or acyl group in the benzamides inhibited the reaction due to steric incumbency or due to the presence of electron-withdrawing groups respectively. Study with *N*-protected benzamides revealed the decreasing trend in yield with the increase in the steric bulk of the amide groups. As the steric bulk of the alkyl groups on the arene coupling partners increased, both yield and selectivity was found to decrease. Similarly, presence of electron-deficient arenes resulted in poor yield and selectivity. However, the aryl C–I bond was unstable under the reaction condition as iodobenzene yielded 15% of phenylated product. Moreover, competition experiment revealed electron-rich arenes to react faster compared to electron-deficient arene systems. Generation of electrophilic $Pd(OTf)_2$ served significant as it was identified as the true active catalyst that would efficiently coordinate with the amide carbonyl group. Oxidation of the Pd(II) species to a cationic Pd(IV) intermediate was carried out by the oxidant $K_2S_2O_8$ which would undergo a facile C–H activation with high *para*-selectivity.



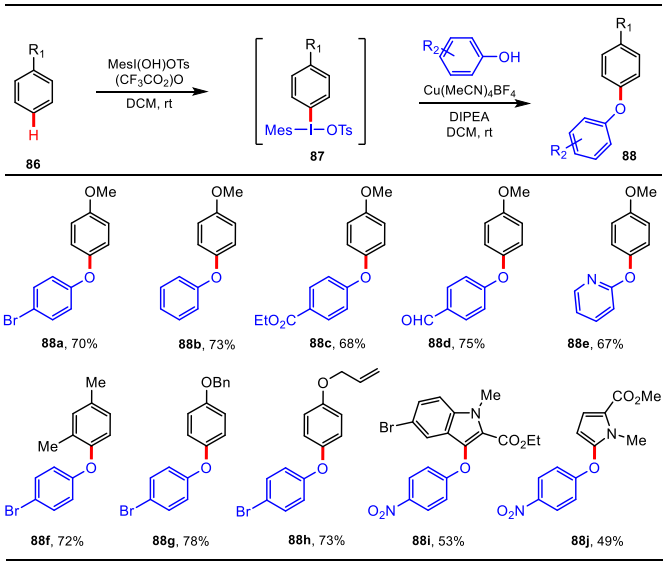
Scheme 21: Palladium catalyzed *para*-arylation of monosubstituted arenes with tertiary benzamides as coupling partners.

Later in the same year, Suna and coworkers reported a Cu(I) catalyzed *para*-amination protocol of arenes (Scheme 22).[49] This was an advancement over their earlier reported sp^2 C–H amination of heteroarenes in which *para*-amination was limited only to the substrates with electron-releasing groups and thus suffered from narrow scopes and moderate yields.[50] This protocol highlighted the use of an unsymmetrical diaryl-λ^3-iodane intermediate as a partner in promoting facile two-step one-pot *para*-amination of arenes with *N*-unprotected amines. Starting with o-xylene along with equivalent amount of 2,4,6-triisopropylphenyl (TIPP) group-containing iodonium reagent TIPP-I(OH)OTs in presence of strong acid additives such as TsOH and TfOH, 10 mol% of $Cu(MeCN)_4BF_4$ as the catalyst, stoichiometric amounts of DIPEA as the base and with a combination of MeCN:DMSO (1:4) as solvent, *para*- aminated arenes were obtained with high regioselectivity and in excellent yields (upto 80%). The reaction was archetypal of electrophilic substitution reaction and takes place at the positions *para*- to the strongest electron-donating substituents on the arene ring. Substrate scope revealed tolerance towards a variety of functional groups including *O*- and *N*-protected groups. Notably, C–H amination of 6-MeO-tetrahydroisoquinoline also proceeded with appreciable regioselectivity. Synthetic utility was further shown by the synthesis of antibiotic Linezolid. Cu(I) salts were presumed as the active catalytic species and Cu(II) salts were *in situ* reduced to the Cu(I) state by the amine. This was corroborated by the higher efficiency of $Cu(MeCN)_4BF_4$ complex compared to other Cu(II) complexes. Subsequently, a Cu(I)/Cu(III) catalytic cycle was presumed to be operative for the concerned transformation.



Scheme 22: (A) Copper catalyzed *para*-amination of aromatic arenes (B) Synthesis of antibiotic drug Linezolid.

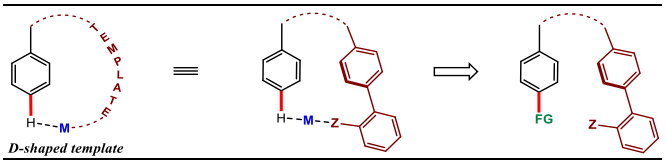
Subsequently, Suna and coworkers revealed the reaction of electron-rich arene or heteroarene ligands of unsymmetrical diaryl-λ^3-iodanes with phenolates (Scheme 23).[51] Previously, oxygen nucleophiles like phenol were found to react with the electron deficient aryl moiety of the unsymmetrically substituted diaryliodonium species and not with the electron rich counterpart.[52] Suna solved the challenge by employing a a Cu(I) catalyzed reaction condition which was used to perform a one-pot, two-step sequential catalytic C–H aryloxylation. Initial reaction of the electron-rich arene or heteroarene with MesI(OH)OTs furnished the diaryl-λ^3-iodanes. Reaction of the latter with phenolates under a Cu(I) catalyzed reaction condition led to the formation of diarylethers with excellent *para*-selectivity. Regioselectivity of the reaction was decided during the formation of the λ^3-iodanes. However, the same in case of heteroarenes fell in line with the traditional S_EAr mechanism. The reaction proceeded under room temperature and displayed excellent functional group tolerance. This strategy was therefore complementary to transition-metal catalyzed C–O bond formation that requires arenes with a preinstalled *ortho*-director.[53]



Scheme 23: Copper catalyzed *para*-aryloxylation of aromatic arenes.

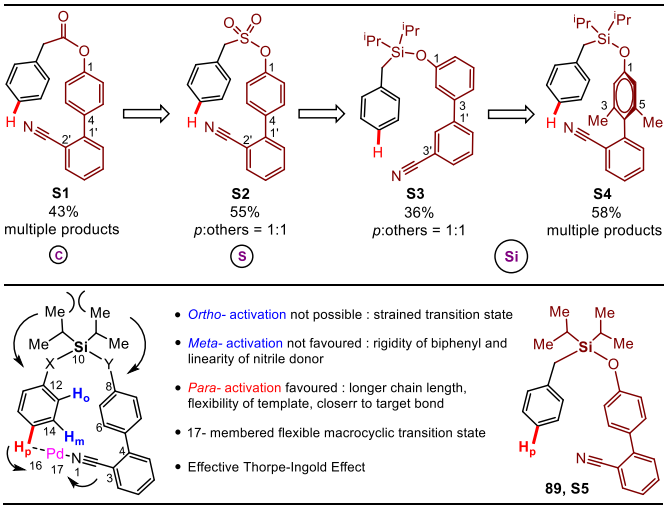
3. Template mediated remote *para*-C–H activation

Over the past few years, enormous volume of scientific exertion has been pledged to develop a promising strategy for selective activation of the *para*-C–H bond. Prevailing strategies for *para*-functionalization was contingent on use of electronic or a steric based approach which was often limited by fewer substrate scopes, lower yields and poor regioselectivity. Moreover, a brisk re-assessment of the previous results reveals most of them to be confined by a narrow scope of functionalization *e.g.* biaryl formation. Also, some of these strategies pre-requisite an *ortho*-chelator as a handle to effectuate a chelation strategy in improving the selectivity. Hence, such drawbacks required a myriad of improvements to solve the long standing challenge of *para*-C–H functionalization with uncompromised yields and selectivity.



Scheme 24: *Para*-C–H functionalization of aromatic arenes in presence of a directing template.

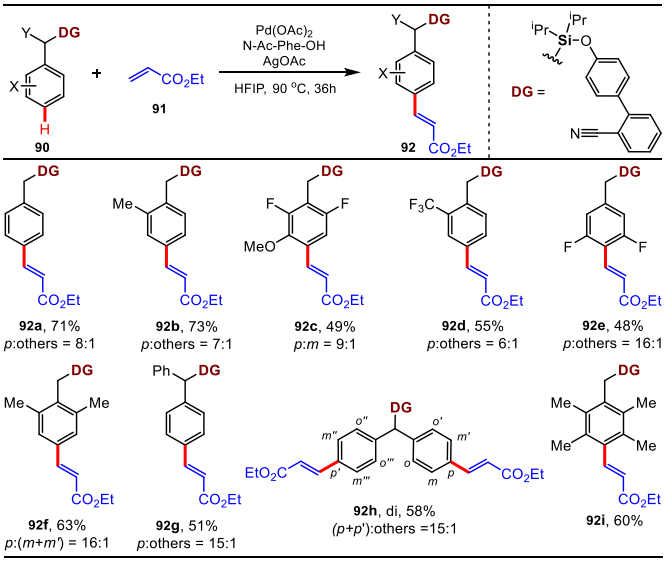
Few years back, efficacy of a directing group facilitated *meta*-C–H transformation were pioneered by Yu and co-workers.[3] Coherent to this, Maiti and co-workers had also adopted the template based strategy and extended its utility in performing *meta*-C–H olefination, acetoxylation and hydroxylation of aromatic substrates.[54] In 2015, Maiti independently presented his report on a D-shaped template (Scheme 24) based remote *para*-C–H activation of toluene derivatives by a systematic engineering of the structure of the directing group.[5] In this report, versatility of a directing group was shown to facilitate selective activation of the *para*-C–H bond in an arene irrespective of its remote location from the local functional group. Applicability of such a directing group based strategy in *para*-functionalization had remained elusive owing to the difficulty in the formation of the required macro transition state while activating the distal located C–H bond. This difficulty could be attributed to the increase in the ring strain that forbid formation of the macrocycle. Additionally, care was required to prevent unwanted activation of the *ortho*- or *meta*-C–H bonds in presence of the donor group. As a result, implementation of the strategy sought for a prior address of some important concerns. First, conceiving a large yet less-strained macrocyclic transition state. Activation of the *meta*-C–H bond using the directing group approach solicits a metallacycle much larger than a seven-membered ring. Obviously enough, reaching out to the even far-located *para*-C–H bond would mean a rise in the size of the metallacycle relative to that required for *meta*-C–H activation with a concomitant rise in the strain energy. Secondly, attaining the necessary size of the macrocycle would entail a prudential monitoring of the chain length to facilitate functionalization at the *para*-position. Third, governing the proximity of the coordinating group in the template in order to allow a simplified delivery of the electrophile towards the target bond of interest through a conformationally flexible assembly. Increased electrophilicity of the coordinated metal assures a ready C–X bond formation *via* agostic interaction. This could relax the entropy demand of the macrocyclic pre-transition state as well as compensate the enthalpic cost of cleaving the thermodynamically stable C1–H bond.



Scheme 25: Screening of directing groups for remote *para*-C–H activation of aromatic arenes.

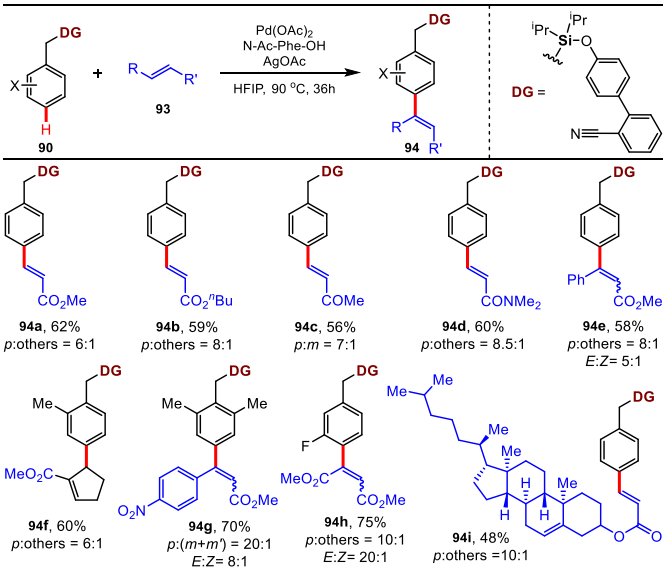
Optimization of an array of scaffolds led to the biphenyl group serving as a vital part of the template chain (Scheme 25). Besides providing the optimum chain length, it induced rigidity into the template skeleton thus nullifying *ortho*-/*meta*-C–H activation since the cyclophane assembly in such cases would now be kinetically disfavoured. A proper choice of the tether was essential for attaining the desired selectivity. Carbonyl and sulphonyl tether were employed as trials for the tether linkage. Both failed to provide any desired selectivity. Following investigation with a range of tether linkage, one of the biphenyl rings was attached to the substrate using a di-isopropyl substituted silyl centre. The other ring carried the coordinating donor. Presence of this silicon centre ensured an elongated silicon-carbon and silicon-oxygen centre that would help in assuring an optimum distance between the target C–H bond and the donor. Installation of the sterically hindered iso-propyl groups induced a 'Thorpe-Ingold' effect that allowed closer approach of the coordinating group to the *para*-C–H bond by a domino-like 'Steric-Push'. A further installation of methyl groups at the 3,5- positions of **S4** did not provide substantial *para*-selectivity as increased steric demand disfavoured coordination of the ligand with the metal electrophilic metal centre. Finally, **S5** was recognized as the effective scaffold for the remote *para*-C–H activation. With the optimized scaffold structure in hand, *para*-C–H olefination reaction was tested on toluene using $Pd(OAc)_2$ as the catalyst, Ac-Phe-OH as the ligand

and AgOAc as the oxidant in HFIP as the solvent at 90 °C for 36 hours. *Para*-C–H olefinated product was obtained in 71% isolated yield with an excellent ratio of 8:1 (*para*:others) (Scheme 26). The observed result was further corroborated by performing control experiments which indicated a complete loss in the *para*-selectivity. This justified the role of the template design and the necessary electrophilic coordination of palladium by the donor group as the pre-requisites for the concerned protocol. Both olefination and acetoxylation were performed with good to excellent *para*-selectivity. Substrate scope comprised of arenes with both electron-donating as well as electron-withdrawing groups which provided good yields along with exquisite levels of *para*- selectivity.



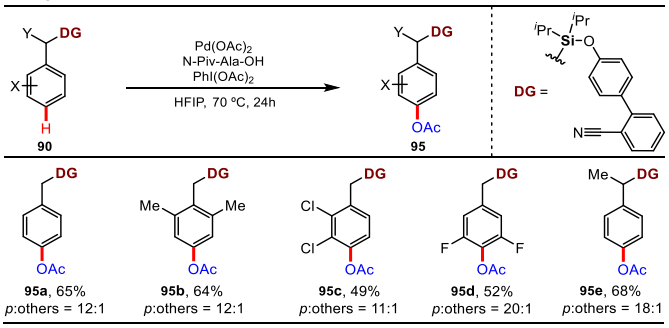
Scheme 26: Palladium catalysed template assisted *para*-olefination of toluene derivatives.

A variety of olefins such as *α,β*- unsaturated esters, sulfone and amides along with bulky acrylates like that of vitamin E were also found to be compatible under the newly discovered protocol. *Para*-olefinated products were obtained with cyclic rings containing endocyclic double bonds (Scheme 27). Regioselective *para*-acetoxylation of toluene was also performed using this template assisted strategy that proceeded with good yields and excellent *para*-selectivity (Scheme 28).



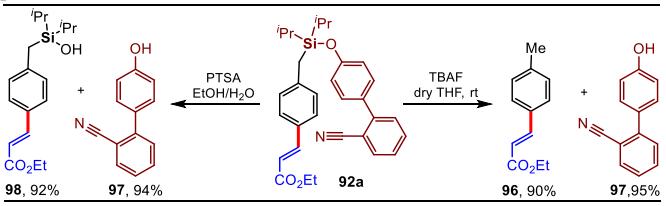
Scheme 27: Palladium catalysed template assisted *para*-functionalization of toluene with olefin derivatives.

Alkanoyl protected amino-acid facilitated chelation of the dianionic ligands with the metal for generating an active pre-catalyst. With its presence as an internal base, it also expedites the C–H activation step. Stabilization of the macrocyclic transition state was affected by coordinative interaction of fluorinated alcohols with the palladium catalyst.



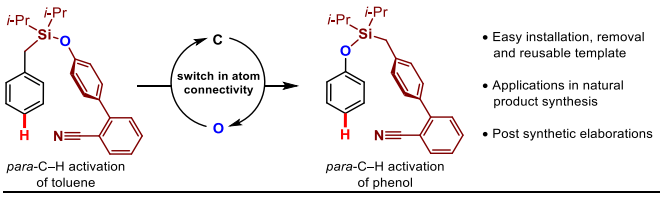
Scheme 28: Palladium catalysed template assisted *para*-acetoxylation of toluene derivatives.

Cleavage of the template was performed by either TBAF or under acid-catalyzed deprotection conditions allowing recovery of the nitrile containing directing group (Scheme 29). Hence, a template based strategy was successfully conceived that could overcome the existing shortcomings and facilitate a highly selective *para*-functionalization protocol.



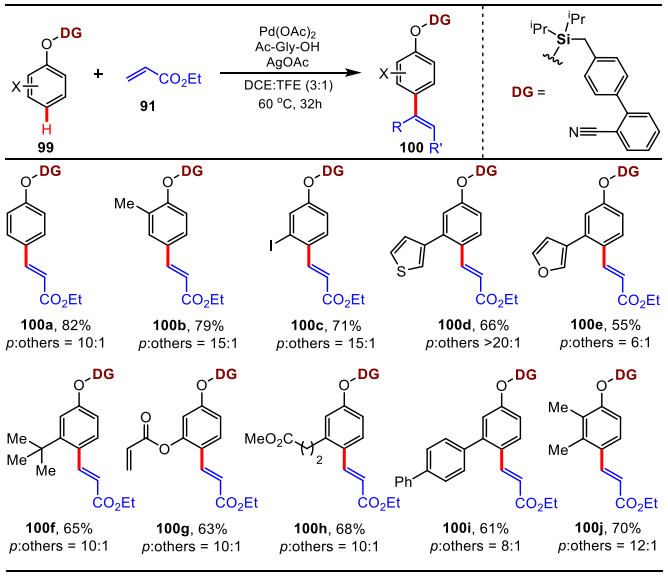
Scheme 29: Cleavage of the directing group under different conditions.

Recently in 2016, Maiti disclosed the efficacy of the benign silyl-biphenyl template based model in performing *para*-C–H olefination of phenols.[55] With a switch in the atom connectivity in the previously reported scaffold (Scheme 30),[5] a functionally operative directing group for *para*-C–H activation of phenol was obtained.



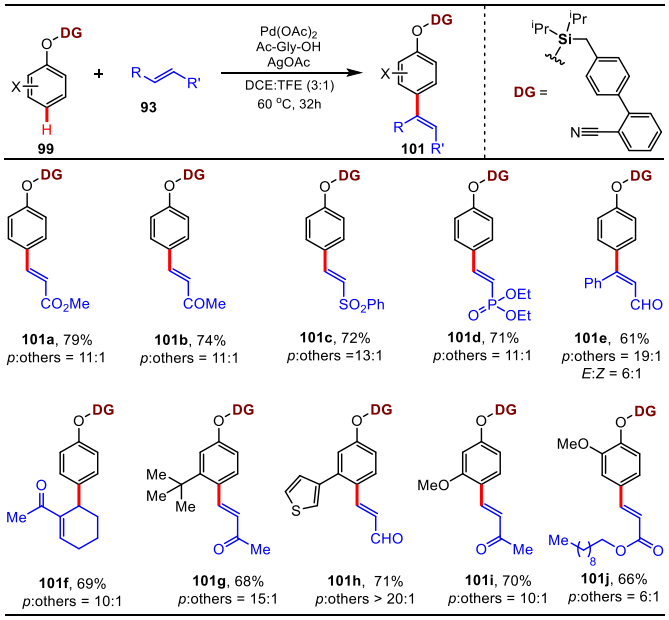
Scheme 30: Template design for *para*-C–H activation of phenol.

This easily recyclable and traceless directing group was suitable in bringing the weakly held electrophile to the target bond through the cyclophane 17-membered transition state. Significance of the template was highlighted in its simplicity, ease of preparation and ability to overcome the innate strain in formation of the macrocyclic assembly at the transition state. With Ac-Gly-OH as the ligand and AgOAc as the oxidant, a palladium catalysed olefination was performed with **99a** in combination of DCE and TFE (3:1) as the solvent at 60 °C (Scheme 31,32).



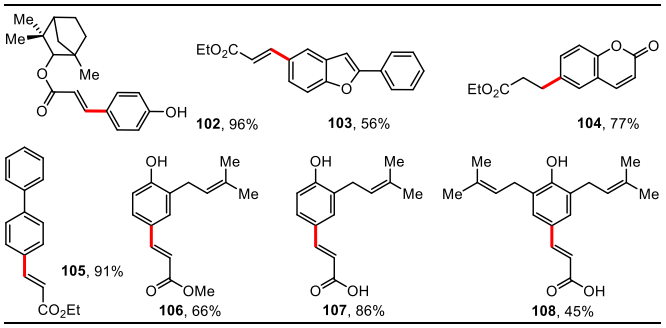
Scheme 31: Palladium catalysed template assisted *para*-olefination of phenol derivatives.

A 10:1 selectivity in favour of *para*-C–H olefination was obtained with 82% isolated yield. Controlled experiments in absence of the coordinating heteroatom were also performed that emphasized the necessity of the donor heteroatom in the directing template.



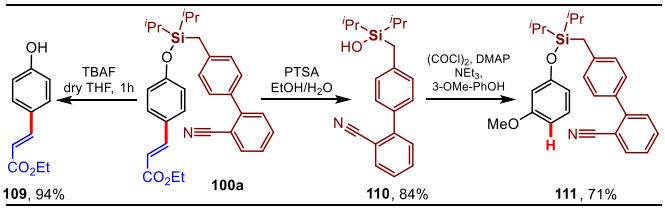
Scheme 32: Palladium catalysed template assisted *para*- functionalization of phenol with olefin derivatives.

Novelty of the protocol was further demonstrated by synthesis of phenol-based natural products and complex molecules. Late-stage functionalization of the phenol and the ethylcarboxylate centre paved way for the synthesis of several complex molecules such as **102**-**105**. Synthesis of several complex moieties as well as drug molecules such as anti-microbial plicatin **106**, drupanin **107** and anti-inflammatory artepellin C **108** were also performed utilizing the benign methodology (Scheme 33).



Scheme 33: Late-stage modification of *para*-functionalized phenol derivatives.

Insitu cleavage of the template could be performed with TBAF to provide *para*-functionalized phenols in good yields. However, treatment with *p*-toluenesulphonic acid generated the silanol **110** which could be re-installed separately for another event of *para*-functionalization (Scheme 34).



Scheme 34: Removal of the directing group under different conditions.

3. Conclusion

The last decade bears testimony to one of the unprecedented accomplishments in the history of C–H functionalization. Significant efforts were made in reaching beyond the conventional sites of functionalization in an aromatic core. Installation of functionalities at the *para*-position of aromatic rings has helped in augmenting the applicative potential of these molecules in various fields of interest. With regard to this, implementation of these newly established strategies in effectuating the synthesis of *para*-functionalized molecules will open up new gateways in expediting the access to these specialized molecules. Moreover, revelation of the template based *para*-C–H activation strategy has enabled transformation of the remotely located *para*-C–H bonds in association with excellent degree of *para*- selectivity. However, significant developments are still to be executed for expanding the scope of functionalization. This will necessitate a deeper perception of the mechanistic details, reaction conditions, substrate nature and application of the methodologies in practical set up.

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Notes and references

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