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Utilization of methylarenes as versatile building blocks in organic synthesis

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Utilization of methylarenes as versatile building blocks in organic synthesis

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The development of practical and efficient methods for C–C and C-X bond formation has attracted a great deal of current attention with the advent of C-H functionalization reactions. Hydrocarbons are perhaps the most inexpensive and readily available material, and utilisation of such materials for the synthesis of essential chemicals is virtually and economically pragmatic. The means to utilize easily accessible hydrocarbons not only represent a useful, potent and straightforward alternative, but also constitute an excellent opportunity to improve our chemical knowledge about a relatively unexplored domain. Early examples using alkylarenes are generally limited to its conversion to aldehydes, carboxylic acids, and nitriles. This review intends to focus on the latest developments adopting modern strategies on sp^3 C–H functionalization of methylarenes to achieve diverse range of important organic compounds.

1. Introduction

The development of efficient methods for the direct conversion of C-H bond into C–X (X = C, Heteroatom) bond remains a significant challenge in organic chemistry.[1] Mild and selective transformations of this type will find extensive applications across the chemical sciences, including the synthesis of pharmaceuticals, natural products, agrochemicals, polymers, and commodity chemicals. Sustainable chemistry is the present day demand of the society. Developing new synthetic methodologies and novel reaction conditions without compromising product selectivity, energy efficiency, and environmental safety has become the main theme of the current chemical research.[2] Hydrocarbons, derived from oil and natural gas, constitute the most inexpensive and readily available material for chemical industries. Therefore, direct construction of C–C and C–X linkage via carbon-hydrogen (C–H) bond activation of hydrocarbons is of enormous implication, and has currently emerged as a stimulating and challenging topic. In this context, selective functionalization of sp^3 C–H bonds of hydrocarbons e.g. alkylarenes, to value-added products is of crucial importance. Toluene, the simplest and readily available alkylarene, has been catalytically converted into oxidized products such as benzyl alcohol, benzaldehyde, and benzoic acid.[3] Benzonitrile and cyanopyridines are also effectively produced by catalytic ammoxidation of toluene and methylpyridines respectively. The products like alcohols, aldehydes, carboxylic acids, and nitriles are extremely important as versatile intermediates in the commercial manufacture of pharmaceuticals, agricultural chemicals, perfumes, dyes, solvents, and specialty chemicals.[4]

This review is aimed at the state-of-the-art of the rapidly expanding area of research on benzyl sp^3 C–H bond activation. Specifically, recent advances on C–X bond formation utilizing C–H functionalization of methylarenes have been highlighted, with an emphasis to the scope and limitations, and the underlying mechanisms. The report is concluded with a discussion of the likely directions of future research. The focal achievements on the subject matter have been categorized according to the nature of methylarenes input during the course of reaction (Figure 1).

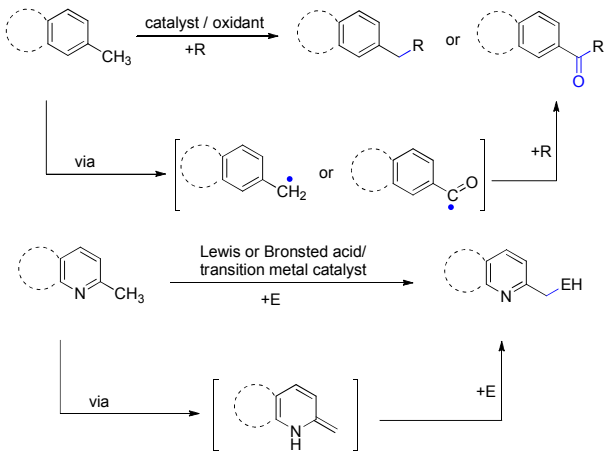

Figure 1 General reaction pathways.

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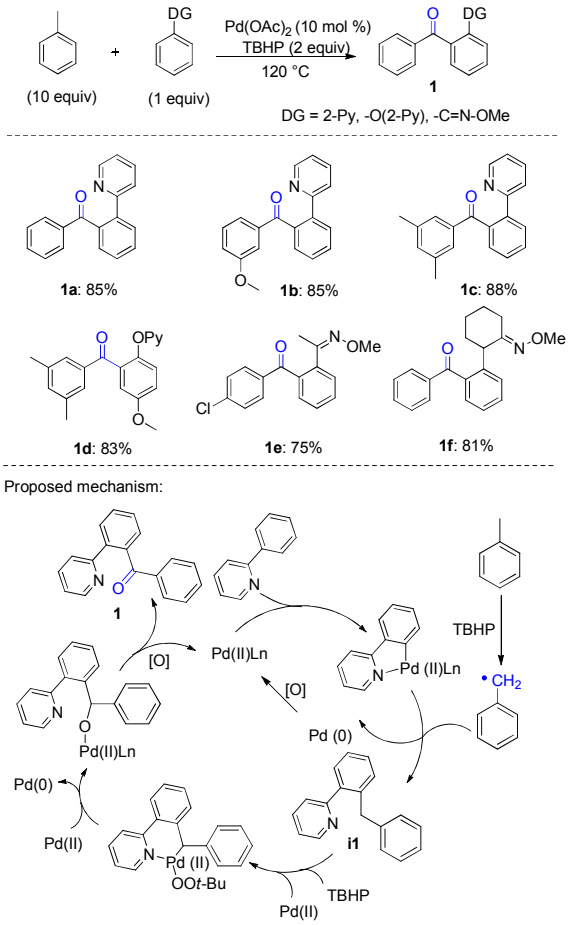
† Footnotes relating to the title and/or authors should appear here. Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

2. Methylarenes as acyl source

Although the conversion of toluene to alcohol/aldehyde is well established, the advent of C–H bond functionalization has led to a new paradigm to transform them into value added chemicals. Toluene C–H bonds can be efficiently employed as acyl surrogate for the synthesis of various useful compounds by means of transition metal catalysts and oxidants.

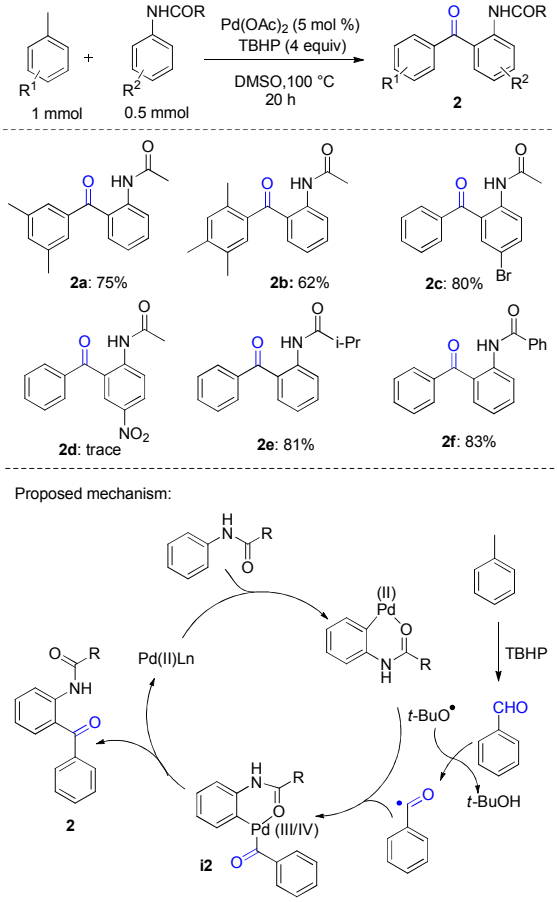
2.1 Synthesis of carbonyl compounds

In 2012, Patel *et al.* have reported an interesting aroylation approach using methylarenes as the acyl source via a Pd(II)-catalyzed cross dehydrogenative coupling (Scheme 1).[6]



Scheme 1 Patel's acylation of various directing groups with methylarenes.

The reaction proceeds through the sequential C–C bond and C–O bond formation by four tandem C-H bond activations (three sp^3 benzylic C-H bonds and one sp^2 arene C-H bond) to selectively install an aroyl moiety at *ortho* position of the substrates containing various directing groups. A blend of $Pd(OAc)_2$ (10 mol %), TBHP (*tert*-butyl hydroperoxide), and alkylarenes (10 equiv) at 120 °C was identified as the optimal to achieve fine conversion. The strategy was successfully applied to various toluene derivatives containing halo, methoxy and polymethylated substituents. Interestingly polymethylated arenes were selectively oxidized to afford mono aroylation product. The proposed mechanism involves TBHP mediated generation of a benzylic radical that undergoes addition to the Pd-substrate complex followed by reductive elimination of the Pd(0) catalyst to afford the benzylated intermediate product (**i1**) which is readily oxidized at its benzylic position to provide the product (**1**).



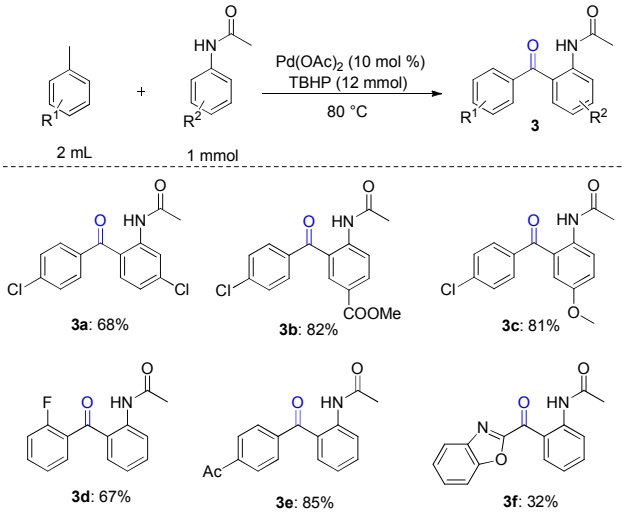
Scheme 2 Sun's acylation of anilides with methylarenes.

In the same year, Sun *et al.* described the ortho acylation of acetanilides (**2**) using Pd(II)/TBHP catalytic system adopting a tandem C–H activation to form *o*-acylacetanilides (Scheme 2).[7] Other oxidants such as H_2O_2, BPO (benzoyl peroxide), DTBP (di-tert-butyl peroxide), $K_2S_2O_8$ and O_2 were found to be completely ineffective. The optimum conditions made use of $Pd(OAc)_2$ (5 mol %) and TBHP (4 equiv) in DMSO at 100 °C for the reaction of methylarenes (2 equiv) and anilide (1 equiv). A key feature of this reaction is the use of reduced quantity of methylarenes (2 equiv). Various methylarenes having the substituents such as halo (**2c**), methyl (**2a**, **2b**) and methoxy are well tolerated during the course of the reaction, but substituents like nitro (**2d**) and acetyl are not compatible. Again, the polymethylated arenes selectively reacted at only one position leaving other methyl groups intact; a possible reason being the pre-oxidation of one of the methyl groups and thus preventing oxidation of the other methyl groups. The proposed reaction pathway comprises the oxidation of toluene

derivatives to the corresponding aldehyde by TBHP and subsequent formation of the acyl radical, which then reacts with the cylclopalladated intermediate of acetanilide to form an intermediate **i2**, which undergoes reductive elimination to afford the product **2** and regeneration of Pd(II) to facilitate the next catalytic cycle.

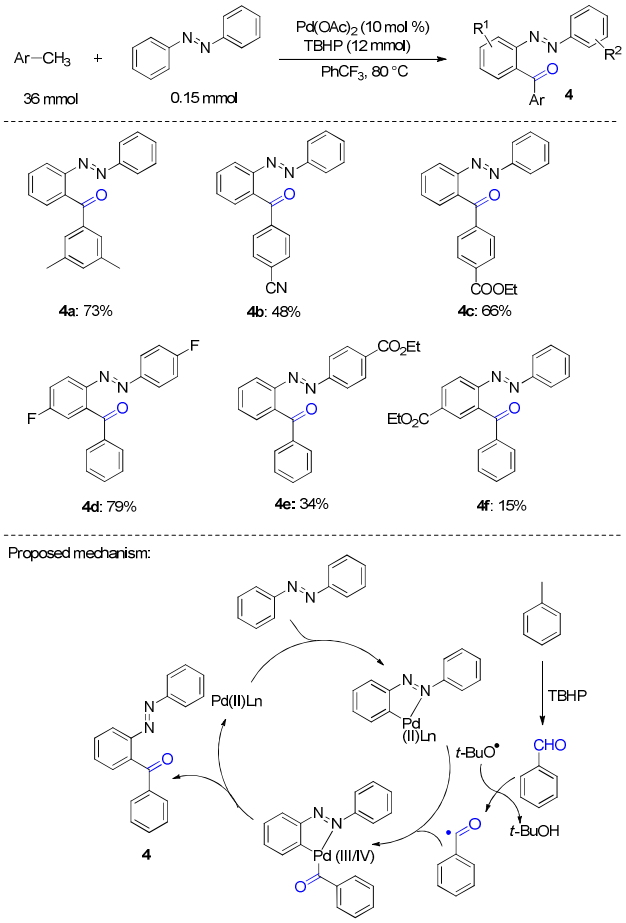
Sun *et al.* later improved the reaction conditions for aroylation of 2-arylpyridines with Pd(II)/TBHP catalytic system involving 2 equivalents of toluene derivatives in DMSO at 90 °C for 24 h.[8]

Kwong *et al.* extended the application of Pd(II)/TBHP catalytic combination for *ortho* acylation of acetanilides (**3**) (Scheme 3).[9] Screening the metal catalysts such as $Pd(OAc)_2$, $Pd(TFA)_2$, $Ni(acac)_2$, and $Rh(PPh_3)_3Cl$ conclusively led to the use of $Pd(OAc)_2$ as the most effective catalyst, whereas TBHP was found to be the most effective oxidant. For each equivalent of anilide and 2 mL of toluene, 10 mol % of the catalyst and 12 equivalents of oxidant at 80 °C were found to be the best. The use of solvents such as 1,2-dichloethane, dioxane, and acetonitrile could not help. Various substituted methylarenes participate in the reaction. The sterically hindered ortho substituted methylarenes also react satisfactorily; whereas polymethyl substituted methylarenes selectively undergo functionalization at only one position. Substituents such as halo (F, Cl, Br), acyl, carboxylic esters and heterocyclic benzaoxazole remain intact during the course of reaction.



Scheme 3 Kwong's acylation of anilides using methylarenes.

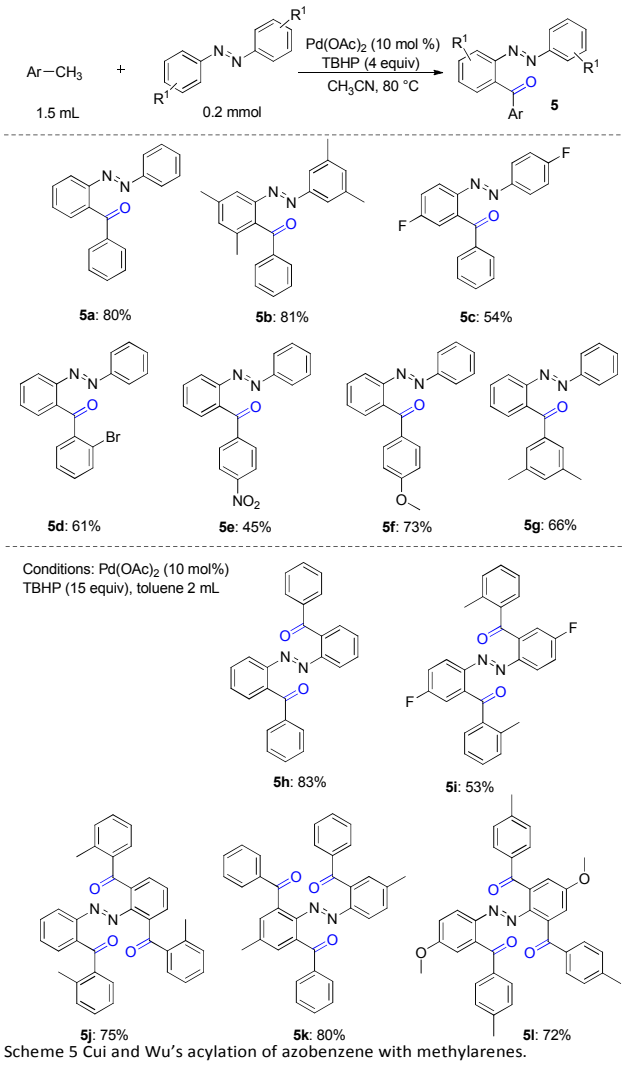
The group of Zeng and Lu has developed a Pd-catalyzed cascade oxidation/sp^2 C-H bond acylation of azoarenes to provide convenient access to a library of *ortho*-acylazoarenes (**4**) using TBHP as oxidant and aryl methanes as acyl source (Scheme 4).[10] After due screening of various catalysts such as $Pd(OAc)_2$, $Pd(TFA)_2$, $PdCl_2$, $PdCl_2(MeCN)_2$, and oxidants such as DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone), MnO_2, $Na_2S_2O_8$, and O_2; 10 mol % of $Pd(OAc)_2$, 12 equiv. of TBHP and 36 equiv. of toluene were found to be ideal for each equivalent of azobenzene in $PhCF_3$ as solvent at 80 °C. Both electron withdrawing and donating substituents are well tolerated; substrates bearing electron withdrawing substituents such as nitro, acetyl, cyano (**4b**), and carboxylic ester (**4c**) gave good yields. The electronic effect of various substituents has been investigated to influence the regioselectivity of the *ortho* acylation of unsymmetric azoarenes, the *ortho*-acylation mainly took place on the electron-rich azo aromatic rings (**4e**). Reaction of 3-azopyridine, however, failed. The strategy has been successfully demonstrated to synthesize a Liver X receptor antagonist. A plausible mechanism is also proposed by the authors based on some control experiments.



Scheme 4 Zeng and Lu's acylation of azobenzene.

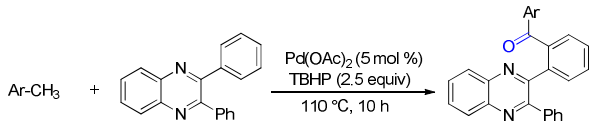
Cui and Wu have reported a practical procedure to acylazobenzene (**5**) via Pd(II)-catalyzed direct regioselective oxidative acylation of azobenzenes with toluene derivatives (Scheme 5).[11] Various mono- and diacylazobenzenes are obtained depending on the amount of oxidant used. Mono acylation of azobenzene was achieved using 10 mol % of $Pd(OAc)_2$ in presence of 4 equivalents of TBHP in CH_3CN at 80 °C, whereas the diacylation of azobenzene requires 15 equivalents of TBHP with no additional solvent at 80 °C for 24 h. Toluene derivatives with both the electron-deficient as well as electron-rich substituents participate effectively; *para*-substituted toluenes gave higher yields than those with *ortho*-substituted, possibly due to the steric hindrance. Azobenzenes with electron-donating groups gave better yields than those

containing electron-withdrawing groups. Interestingly, azobenzenes containing electron-withdrawing substituents (F, Cl) mainly afford the diacylazobenzenes, while triacylazobenzenes were obtained as the chief product for those having electron-donating groups (CH_3, CH_3O).



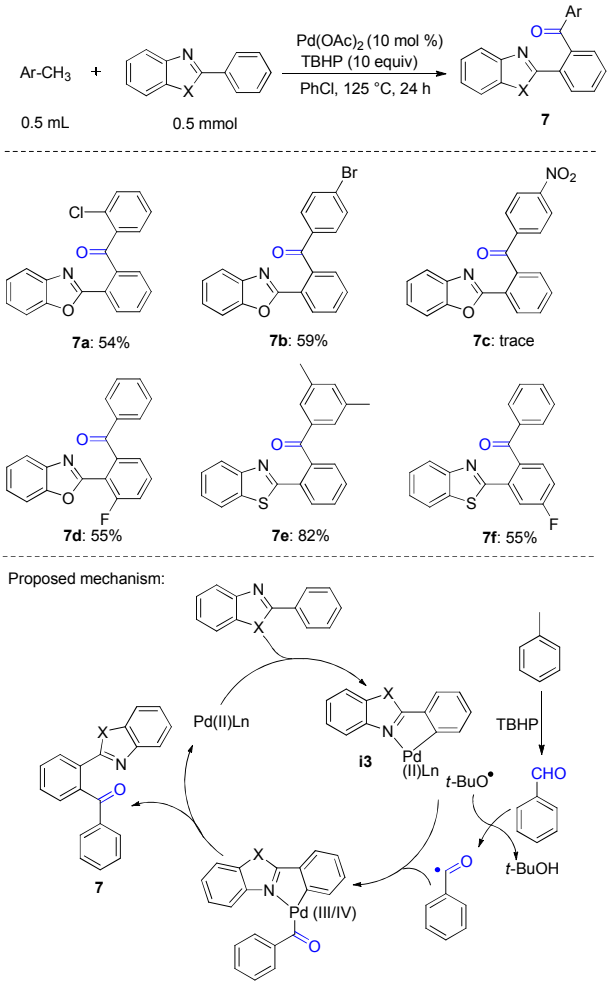
Scheme 5 Cui and Wu's acylation of azobenzene with methylarenes.

In 2014, Patel *et al.* described a 2,3-diarylquinoxaline directed mono *ortho*-aroylation protocol using aromatic aldehydes or alkylbenzenes as aroyl surrogates (Scheme 6).[12] Out of the four available *ortho* sp^2 C-H bonds in the two aryl rings of 2,3-diarylquinoxaline, only one of the C-H bonds is selectively *ortho*-aroylated. In case of aldehyde as aroyl surrogate, the reaction proceeds via an aroyl radical, whereas the use of alkylbenzene as aroyl surrogate proceeds through an aroyl radical or a benzyl radical pathway.



Scheme 6 Acylation of 2,3-Diarylquinoxaline.

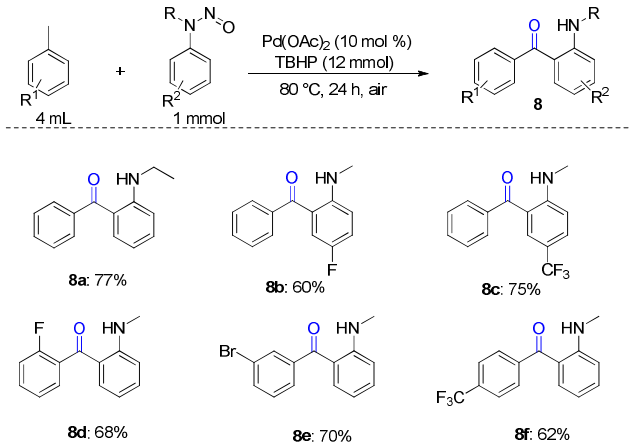
Xuan *et al.* have recently reported a palladium-catalyzed oxidative *ortho* acylation of 2-arylbenzoxazoles and 2-arylbenzothiazoles using TBHP as oxidant with excellent regioselectivity (Scheme 7).[13] The optimum conditions involve the use of 10 mol % of $Pd(OAc)_2$ and 10 equivalents of TBHP in chlorobenzene at 125 °C for 24 h. Toluene derivatives with electron-donating groups afford better yields as compared to substrates bearing weakly electron-withdrawing groups such as Cl and Br. The presence of strongly electron-withdrawing groups such as NO_2 and acetyl, however, inhibit the reaction. 2-Arylbenzothiazoles with different substituents on the phenyl ring have been successfully employed to afford the corresponding acylated products. Based on control experiments, a plausible mechanism involving acyl radical and cyclopalladated intermediate (**i3**) has been outlined by the authors.



Scheme 7 Acylation of 2-arylbenzoxazoles and 2-arylbenzothiazoles with methylarenes.

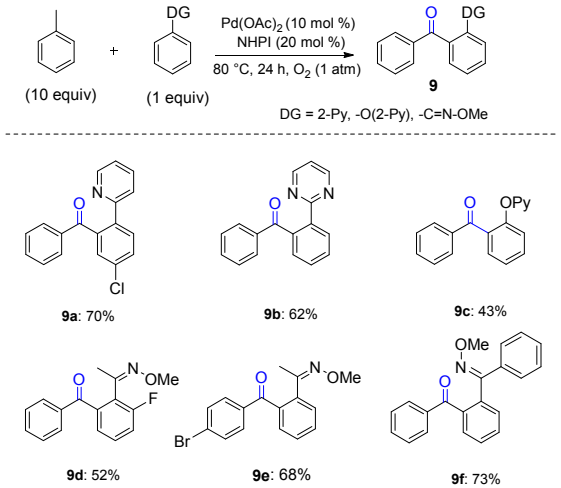
Kwong and Luo have introduced the use of $Pd(OAc)_2$ and TBHP combination for the direct synthesis of *N*-alkyl-2-aminobenzophenones (**8**) by cascade cross-coupling of *N*-nitrosoanilines and toluene derivatives (Scheme 8).[14] The nitroso group behaves as a traceless directing group, whereas methylarenes act as acyl precursor. Fluoro, bromo, chloro,

methoxy, and trifluoromethyl groups at different positions are compatible in this reaction to afford an array of *N*-alkyl-2-aminobenzophenones. Based on control experiments and GC-MS analysis, the authors have proposed the use of the palladium complex for the aliphatic C–H bond oxidation to aldehyde by the oxidant at elevated temperature, which subsequently generates the acyl radical. The *N*-nitroso group undergoes directed electrophilic palladation to form a palladacyclic intermediate, which then reacts with the acyl radical to afford the ketone product **8**, after reductive elimination and N–N(O) bond cleavage.



Scheme 8 Acylation of *N*-nitrosoanilines with methylarenes.

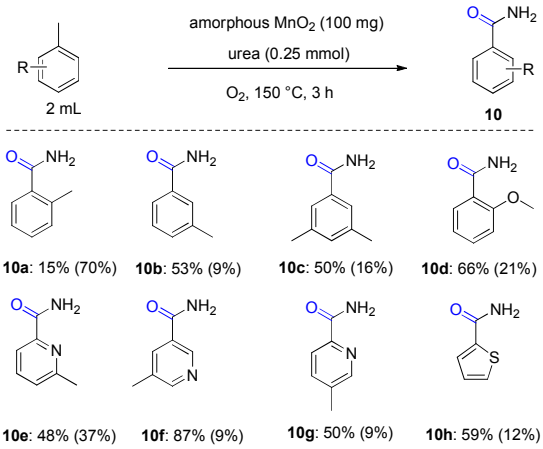
Very recently, Jiao *et al.* reported an elegant approach for the acylation of O-methyl oximes and 2-phenylpyridine derivatives with methylarenes in the presence of $Pd(OAc)_2$ (10 mol %) as catalyst, NHPI (*N*-hydroxyphthalimide) (20 mol %) as co-catalyst, and molecular oxygen as an oxidant in moderate to good yields (Scheme 9).[15] The reaction scope is broad in terms of both coupling partners. The proposed mechanism involves the Pd-catalysed C-H activation steps and formation of acyl radical as active intermediate.



Scheme 9 Jiao's acylation of various directing groups with methylarenes.

2.2 Synthesis of amides.

In 2012, Mizuno *et al.* have developed a novel procedure for the synthesis of primary amides (**10**) by the amorphous MnO_2-catalyzed aerobic oxidative amidation of methylarenes with urea as ammonia source at 150 °C under O_2 for 3 h (Scheme 10).[16] Various methylarenes and even polymethylated arenes can be selectively converted into the corresponding monoamides (or nitriles). Most reactions lead to the formation of nitriles along with aldehydes and carboxylic acids as main byproducts. Besides toluene derivatives with electron-donating as well as electron-withdrawing groups, heteroaromatic methylarenes such as methylpyridine, methylquinoline, methylthiophene derivatives participate in the reaction. Notably, the amidation of 2,5-lutidine mostly occurs on the methyl group at 2-position, due to the possible coordination of pyridine. Proposed mechanism involves the formation of aldehyde and its ammoxidation with urea to afford the nitrile, which subsequently hydrolyses to the corresponding amide.

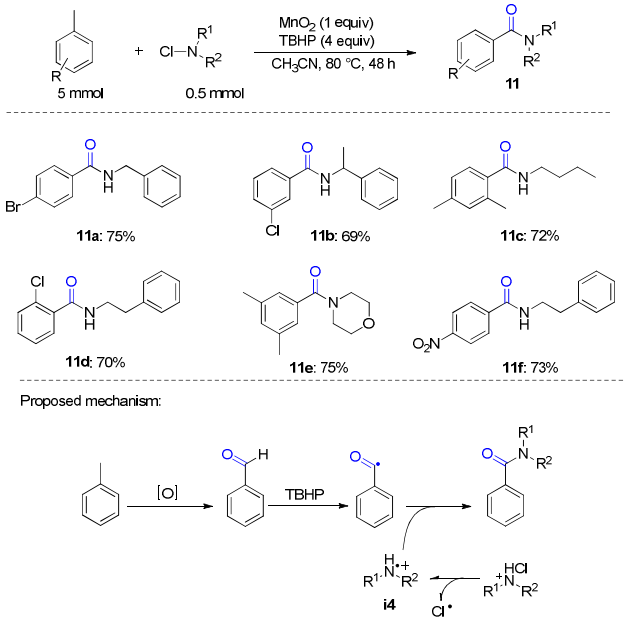


Scheme 10 Mizuno's amidation of methylarenes (yields of the corresponding nitrile are shown in parentheses).

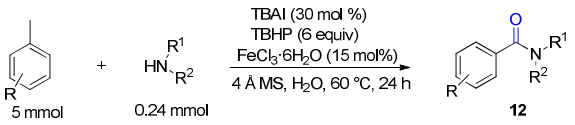
Our group has reported an efficient synthesis of substituted amides (**11**) employing methylarenes and *N*-chloroamines as coupling partners (Scheme 11).[17] Heterogeneous and recyclable MnO_2 was found to be the best promoter. The optimum conditions made use of 1 equivalent of MnO_2, 10 equivalents of methylarenes and 4 equivalents of TBHP for each equivalent of *N*-chloroamine at 80 °C in CH_3CN. All sorts of methylarenes having electron withdrawing as well as elctron-donating substituents participated well in the reaction, although polymethylated arenes are selectively oxidized at only one methyl group. *N*-Chloroamines of both the primary and secondary amines couple effectively. The proposed mechanism involves the oxidation of methylarenes to aldehydes which gives rise to acyl radical by the action of TBHP. The *N*-centred radical (**i4**) generated from *N*-chloroamine eventually combines with acyl radical to give the desired product.

Heydari *et al.* reported the amidation of methylarenes with amine hydrochloride salts employing KI (20 mol %), TBHP (8

equiv), and $CaCO_3$ (1.5 equiv) as catalytic system.[18] Zhao *et al.* applied the use of TBAI (terabutylammonium iodide) (30 mol %), TBHP (6 equiv), and $FeCl_3·6H_2O$ (15 mol %) as catalytic system for the amidation of methylarenes employing free amines (Scheme 12).[19] The reaction scope is broad with moderate to good yields.



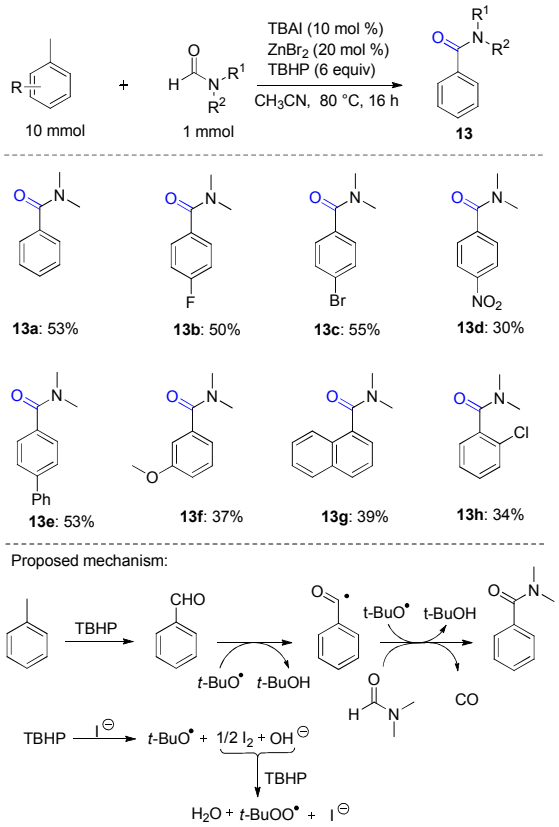
Scheme 11 Singh's amidation of methylarenes.



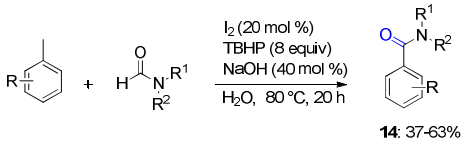
Scheme 12 Zhao's amidation of methylarenes.

Wu *et al.* have prepared various benzamides (**13**) in moderate yields via the cleavage of sp^3 C-H bond of methyl arenes with *N*-substituted formamides (Scheme 13).[20] A combination of 10 mol % of TBAI, 6 equivalents of TBHP and 20 mol % of $ZnBr_2$ in CH_3CN leads to the optimum yield of the products. Various substituted methylarenes are employed successfully. Benzylic radical is proposed to be generated by TBAI/TBHP catalytic system which is then oxidized to benzaldehyde via benzyl alcohol. Meanwhile, the *tert*-butoxyl radical picks up hydrogen radical from DMF, followed by the elimination of CO to form the aminyl radical which then reacts with the benzoyl radical formed from benzaldehyde to provide the desired product.

Sun *et al.* have reported a similar method for the synthesis of *N*,*N*-dialkylamides or *N*-alkylamides by using I_2 as a catalyst and *tert*-butyl hydroperoxide (TBHP) as an oxidant in H_2O as solvent at 80 °C for 20 h (Scheme 14).[21] The reaction is compatible with halogens and functional groups like carboxylic acid esters and cyanides.



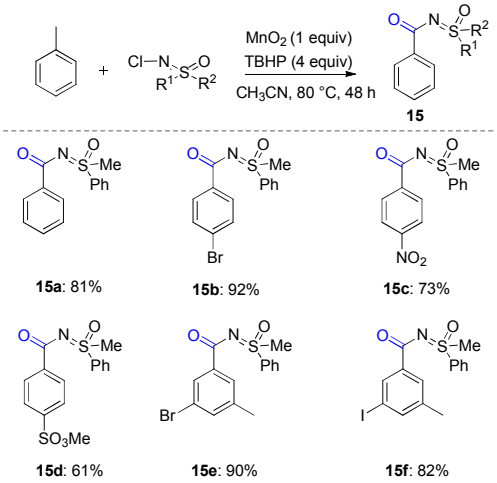
Scheme 13. Wu's amidation of methylarenes using formamides.



Scheme 14 Sun's amidation of methylarenes using formamides.

2.3 Synthesis of *N*-aroyl sulfoximines.

In 2014, Priebbenow and Bolm have reported a new method for the synthesis of *N*-aroyl sulfoximines (**15**) involving the manganese oxide promoted C–H activation of methyl arenes (Scheme 15).[22] A number of *N*-chlorosulfoximines and methylarenes were made to react under the reaction conditions of 1 equivalent MnO_2, 4 equivalents of TBHP in CH_3CN at 80 °C for 48 h to form a series of valuable aroyl sulfoximine derivatives in high yields. Halo substituted methylarenes ensued with excellent yields, groups such as nitro (**15c**) and sulfonate (**15d**) were also tolerated. The proposed mechanism involves the oxidation of methylarenes to aldehydes and then to acyl radical by the action of TBHP. *N*-Chlorosulfoximine furnishes *N*-centred radical which eventually reacts with acyl radical to give the desired products.

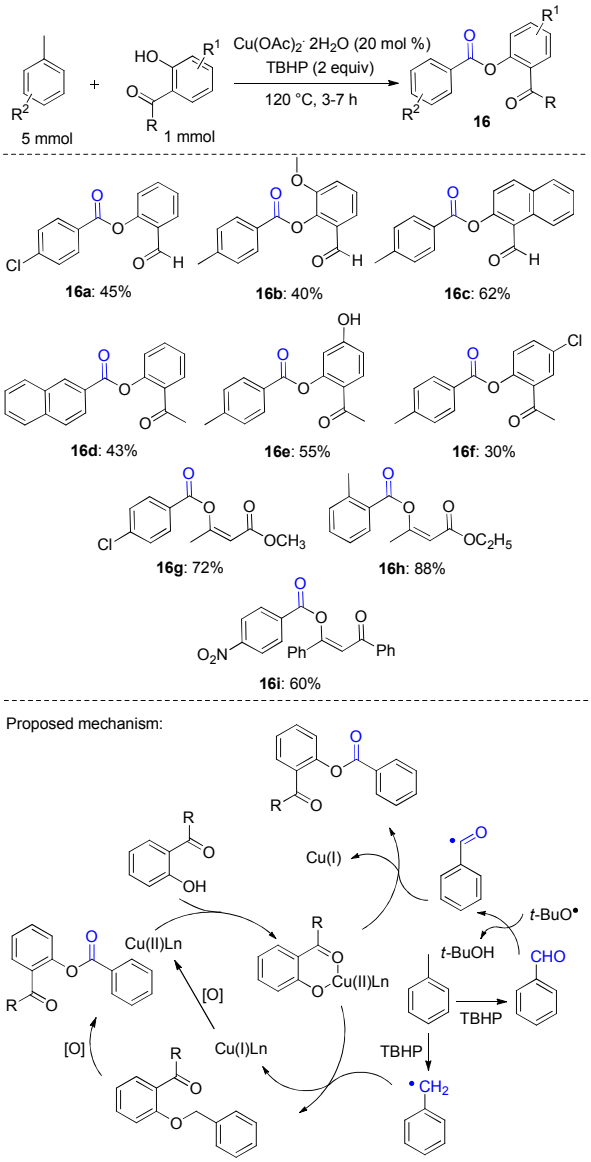


Scheme 15 *N*-Aroylation of sulfoximines.

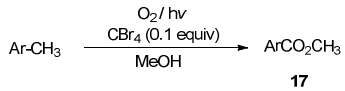
2.4 Synthesis of esters.

Patel *et al.* have developed a directing group assisted copper(II)-catalyzed chemoselective O-aroylation of 1,3-dicarbonyl compounds and phenols by using alkylbenzenes as aroyl surrogates (Scheme 16).[23] Salicylaldehyde resulted in the formation of phenolic ester (**16**) rather than benzylic ester when treated with toluene under oxidative conditions using copper and TBHP; but simple phenol did not react. Methylarenes with electron withdrawing substituents gave lesser yields as compared to the electron-donating group substituted methylarenes. Substrates such as 2-methylpyridine, 3-methylpyridine, and 2-methylimidazole, however, failed to react. Ortho substituted salicylaldehyde gave lesser yield of the desired products due to steric factor. The role of COOH as directing group was also tested but with failure. Electron-donating substituents on 2-hydroxyacetophenones gave better yields of products in comparison to electron-withdrawing substituents. Interestingly in the case of 2,4-dihydroxyacetophenone, the *o*-hydroxyl group was selectively aroylated without affecting the *p*-hydroxyl group (**16e**). The protocol was extended to 1,3-dicarbonyl compounds to acylate its enol form to provide Z-selective enol esters. Based on control experiments, two probable mechanistic pathways are outlined.

Itoh *et al.* reported a photo-oxidative synthesis of aromatic methyl esters from methylarenes via dimethyl acetals using CBr_4 (0.1 equiv) / hν (fluorescent / xenon lamp) and molecular oxygen in methanol (Scheme 17).[24] Methylarenes with electron-donating groups gave higher yields than those containing electron-withdrawing substituents, such as halogen, CN and NO_2. *p*-Xylene got esterified at both the methyl groups. Li and Luque reported esterification of methylarenes using heterogeneous bimetallic Au–Pd catalyst and molecular oxygen as benign oxidant without any additive.[25] Itoh *et al.* reported a photo-oxidative synthesis of aromatic methyl esters from methylarenes via acetals using anthraquinone-2,3-dicarboxylic acid as catalyst. The electron-rich and neutral methyl aromatics were good substrates for oxidative esterification to afford the corresponding methyl carboxylates in high yields; conversely the electron-deficient methyl aromatics containing cyano group proved poor. Ortho substituted substrates led to diminished yields of products.[26]



Scheme 16 Phenolic or enolic acylation using methylarenes.

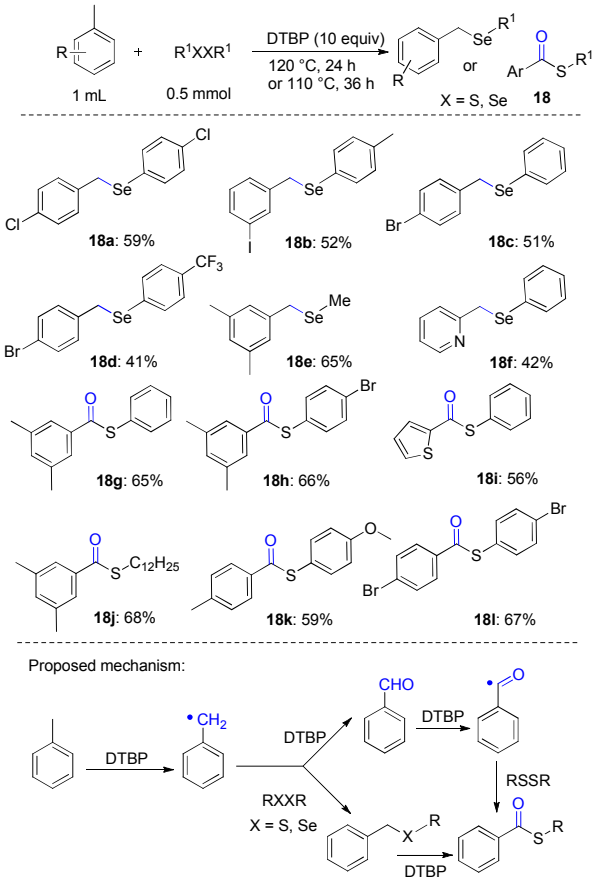


Scheme 17 Photo-oxidative esterification of methylarenes.

2.5 Synthesis of thioesters.

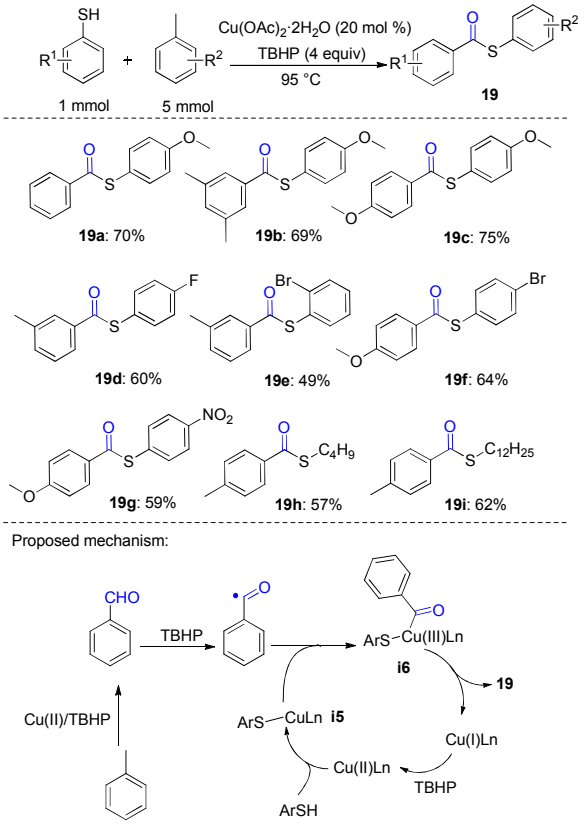
Lee *et al.* have reported a metal-free and solvent-free DTBP (di-*tert*-butyl peroxide) mediated synthesis of selenide ethers and thioesters (**18**) through sp^3 C–H functionalization of methyl arenes with diselenides and disulfides (Scheme 18).[27]

The reaction scope is broad. Interestingly diselenides lead to alkylation whereas disulfides lead to thioester formation. Based on control experiments, authors have proposed a mechanism involving benzyl radical intermediate, which reacts with diselenides or disulfides to give the corresponding ethers. Thioesters are obtained by the oxidation of corresponding ethers or by direct attack of disulfides on acyl radical generated from aldehyde.



Scheme 18 Lee's approach for selenide ethers and thioesters.

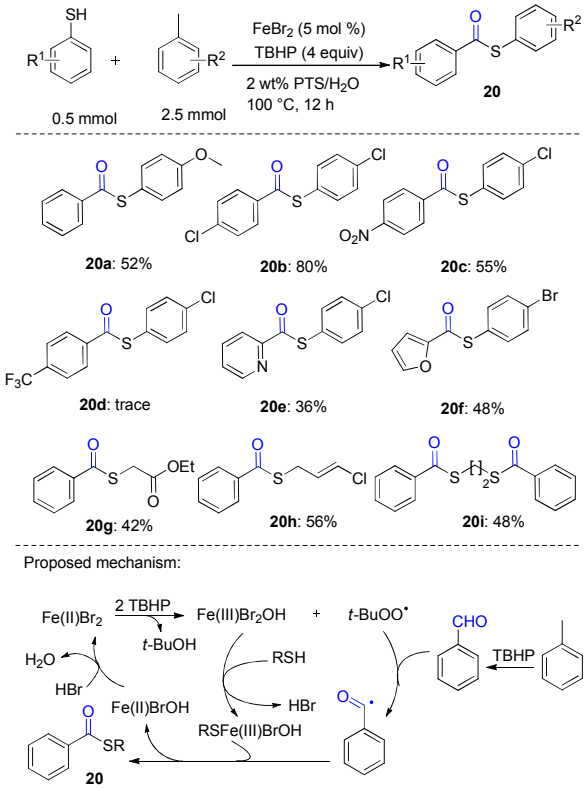
Patel *et al.* have reported a copper catalyzed approach for the synthesis of thioesters (**19**) employing alkylbenzenes and thiols as coupling partners without the assistance of any directing group (Scheme 19).[28] Alkylarenes possessing electron-donating substituents provide good yields of products whereas electron-withdrawing substituent bearing substrates are less effective. Polymethylated arenes are selectively thiolated at only one of the positions. The plausible mechanism postulates the formation of copper thiolate (**i5**), which then reacts with the acyl radical, generated from toluene by the oxidation of TBHP, to give the product via intermediate **i6**.



Scheme 19 Patel's approach for thioesters.

Wang and He have reported the coupling of methylarenes with thiols leading to thioesters (**20**) using $FeBr_2$/TBHP combination in PTS (polyoxyethanyl α-tocopheryl sebacate)/H_2O (Scheme 20).[29] Aryl thiols and methylarenes with different functional groups react smoothly to give the corresponding thioesters. Alkyl thiols viz. benzylic thiol and cyclohexylmethanethiol also show good reactivity, and ethylene mercaptan gave di-thioester (**20i**). Pyridine-, furan-, and thiophene-containing methylarenes also couple effectively with thiols to give the products (**20e**, **20f**).

Li *et al.* have reported a new synthesis of 2-arylquinazolines (**21**) via amination of methylarene sp^3 C-H bonds using potassium iodide as catalyst (Scheme 21).[30] 2-Aminobenzophenone derivatives and methylarenes were made to react with ammonia source in a multi-component fashion to get the desired products. Methylarenes serve as a source of aldehyde. The proposed mechanism is initiated with the formation of benzaldehyde from toluene via radical oxidation in the presence of TBHP. The carbonyl function in benzaldehyde/2-aminobenzophenone reacts with NH_4OAc to give aldimine/ketimine, which after successive cyclization and iodine-promoted oxidative aromatization gives rise to the quinazoline product.



Scheme 20 Wang and He's Iron catalyzed acylation of thiols.

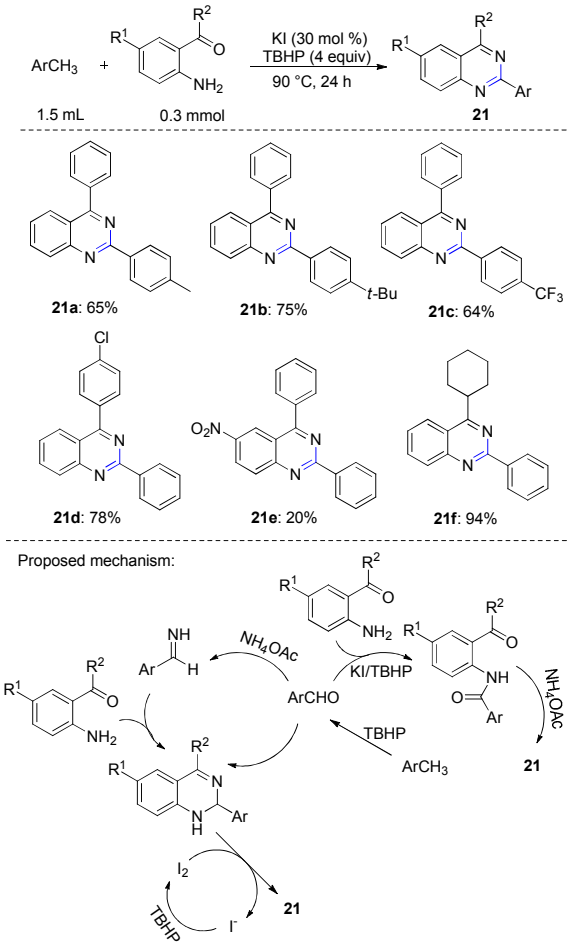
3. Methylarenes as alkyl source.

Toluene sp^3 C-H bonds have been magnificently used as alkyl surrogates for the synthesis of a variety of valuable products.

3.1 Synthesis of nitriles.

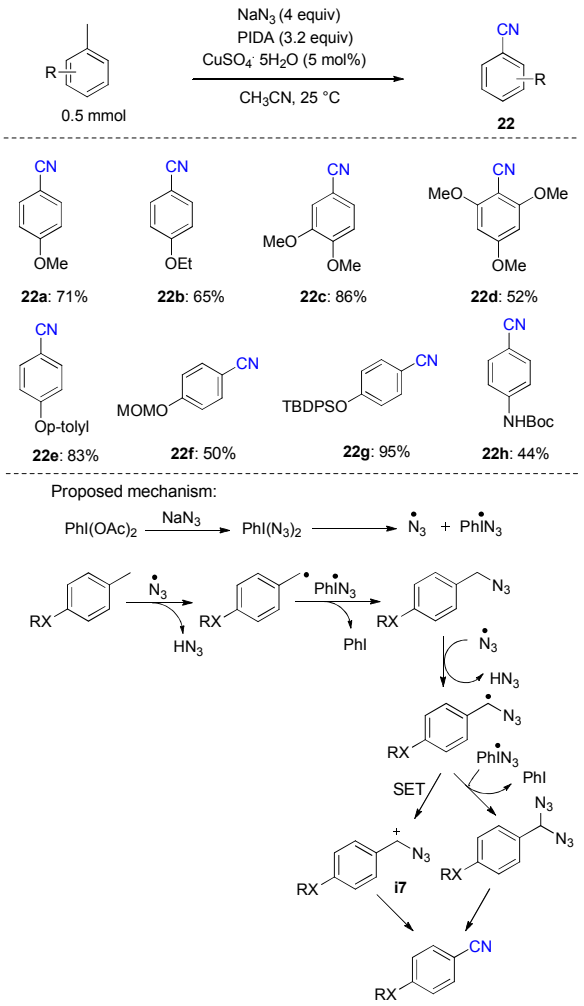
In 2009, Jiao *et al.* reported the synthesis of nitriles (**22**) by the reaction of alkylarenes with NaN_3 as nitrogen source using Cu (II) and phenyliodonium diacetate (PIDA) in acetonitrile at room temperature (Scheme 22).[31] Attempts to use other oxidants such as ceric ammonium nitrate (CAN), $Mn(OAc)_3$, and PhIO were not successful. The presence of *para* substituent on toluene moiety is essential for the reaction as it serves as a directing group. On the basis of control experiments, the authors postulate the generation of benzyl radical by the action of $N_3^{\bullet}$ or $PhIN_3^{\bullet}$ radical which is crucial for the reaction. The subsequently formed benzylic azide undergoes SET process to generate benzylic azide cation (**i7**), which further undergoes Schmidt type rearrangement to give the final product.

Zhang and Wang have developed a palladium-catalyzed ammoxidation of methyl arenes using *tert*-butyl nitrite (TBN) as both the nitrogen source and oxidant (Scheme 23).[32] When *tert*-butyl nitrite (TBN) is employed in the presence of catalytic $Pd(OAc)_2$ and *N*-hydroxyphthalimide (NHPI), the reaction provides the nitrile in 80% yield. When the reaction is carried out in the absence of either TBN or NHPI, product is not observed. The reaction shows a much wider substrate scope and tolerates a wide range of functional groups under mild conditions. Polymethylated arenes are selectively converted to mono-nitrile derivatives; however, with high reagents loading and high temperature, the second methyl group can also be converted into cyano group. To gain an insight into the reaction, authors have conducted radical trapping experiments with TEMPO, which shows complete inhibition of the reaction. Initially NHPI gives rise to the active phthalimide *N*-oxyl (PINO) radical by the action of TBN, which decomposes into NO radical and *t*-BuOH. Benzylic radical is then generated upon hydrogen abstraction by PINO. The reaction of benzyl radical with the NO radical via aldoxime formation finally affords the corresponding nitrile by $Pd(OAc)_2$ catalysis.



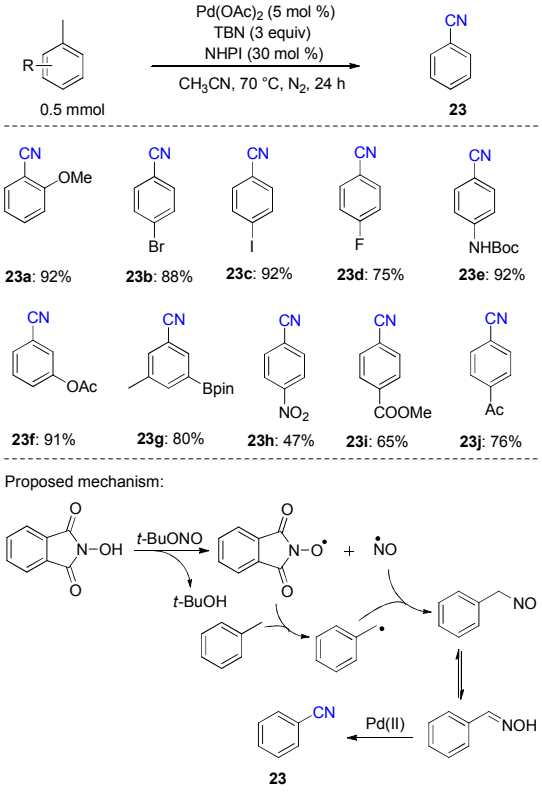
Scheme 21 Li's approach for the synthesis of 2-arylquinazolines.

Togo *et al.* have described a transition-metal-free direct conversion of methylarenes into aromatic nitriles (**24**) by the action of NBS (*N*-bromosuccinimide) or 1,3-dibromo-5,5-dimethylhydantoin (DBDMH) in the presence of a sub-stoichiometric amount of AIBN or benzoyl peroxide (BPO), followed by the reaction with molecular iodine in aq. NH_3 in a one-pot procedure (Scheme 24).[33]

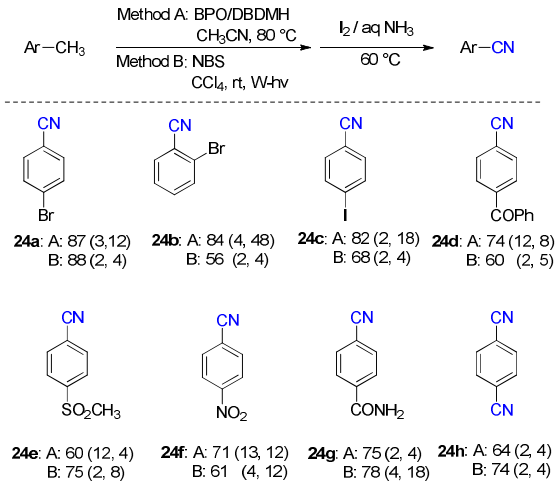


Scheme 22 Jiao's NaN_3/PIDA promoted approach for the synthesis of nitriles.

After systematic screening, two procedures have emerged for the preparation of nitriles; DBDMH with BPO in refluxing acetonitrile (method A) for electron-deficient methylarenes, and NBS under irradiation with a tungsten lamp in carbon tetrachloride at room temperature (method B) for electron-rich methylarenes. Moreover, when method B is used for 2-methoxytoluene and 4-methyl-1,2-dimethoxybenzene with 2.2 equiv of NBS, bromination also occurs. When polymethylated arenes such as *p*-xylene and *m*-xylene are employed, both the methyl groups participate in the reaction using methods A as well as B with twice the amounts of DBDMH or NBS. The proposed mechanism follows the Wohl-Ziegler type bromination of methylarenes to give benzyl bromide, which then reacts with aq. NH_3 to give benzylamine. Benzylamine is finally converted into nitrile with iodine via the formation of imine and *N*-iodoimine. Very recently Cheng *et al.* have illustrated iodine catalysed ammoxidation of methylarenes in the presence of NH_4F and TBHP.[34]



Scheme 23 Zhang and Wang's approach for the synthesis of nitriles.

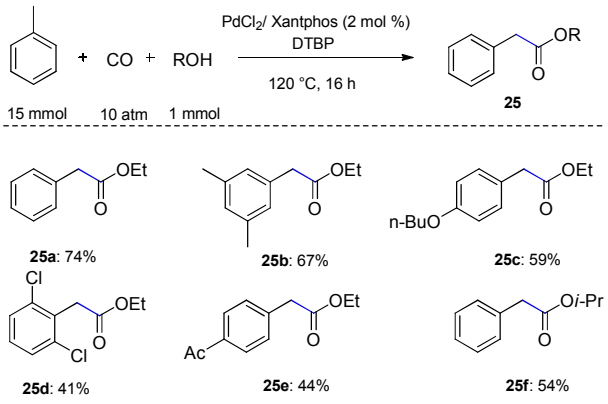


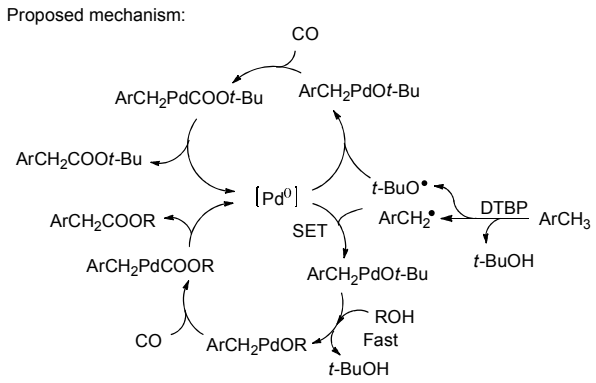
Scheme 24 Togo's approach for the synthesis of nitriles (the values in the parentheses stand for the time in hours).

3.2 Carbonylation reactions.

Toluene can be successfully carbonylated by activating sp^3 C-H bonds selectively without involving arene C-H bonds under oxidative conditions. In 2012, Huang *et al.* developed a new strategy for generating benzylpalladium reactive species from toluene via non-directed C(sp^3)–H activation (Scheme 25).[35] This led to an efficient Pd-catalyzed reaction protocol for the oxidative carboxylation of benzylic C–H bonds to form substituted 2-phenylacetic acid esters and derivatives. They

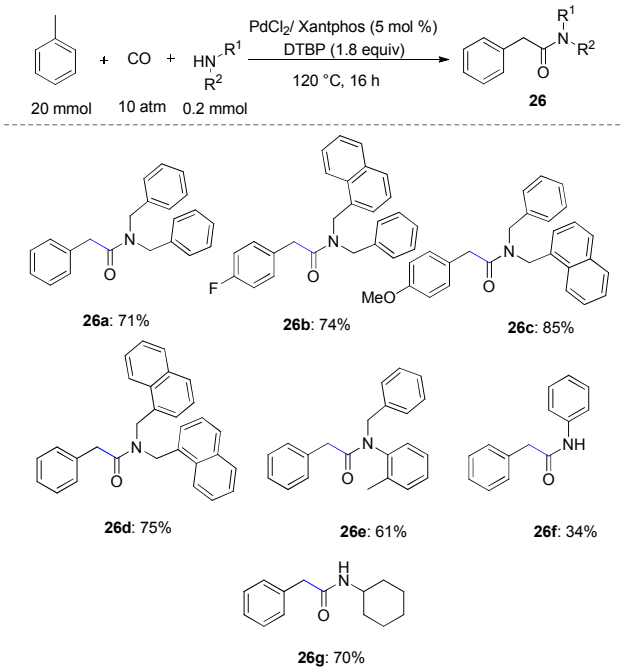
accomplished the oxidative coupling of toluene derivatives with CO and alcohols to afford phenylacetic acid esters (**25**) in the presence of palladium as catalyst and di-*tert*-butyl peroxide (DTBP) as oxidant. The problem of C–H bond activation was solved by the use of DTBP to afford benzyl radical, which when reacts with palladium and oxidant, gives a benzyl palladium species that undergoes carbonylation esterification to afford the product. The most effective combination involves DTBP, $PdCl_2$ and Xantphos in the presence of 10 atm of CO at 120 °C in ethanol. Generally the reactions afford moderate to good yields of products with various substituents. Doubly methyl substituted arenes are selectively carbonylated at only one position.



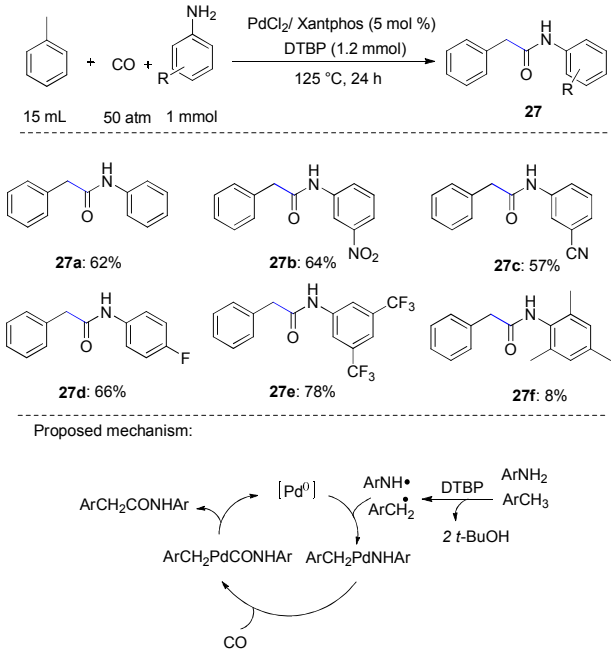


Scheme 25 Huang's carbonylation of methylarenes.

Subsequently, the same catalytic system was applied for the oxidative aminocarbonylation of methylarenes for the construction of arylacetamides (Scheme 26).[36] A combination of 5 mol % of Pd(Xantphos)Cl_2, and 1.8 equiv of DTBP at 120 °C under 10 atm of CO for 16 h was found to be the highest yielding condition. The reaction tolerates a wide range of functional groups, and a series of substituted dibenzylamines successfully participate in the reaction. Sterically hindered amines and methylarenes, however, offer decreased yield of the products. Electron deficient arenes and aniline afford rather low yields of products. When the radical scavenger (TEMPO) is added to the reaction, the carbonylation reaction is inhibited. Authors believe that the aminocarbonylation reaction proceeds via a benzylpalladium intermediate which could be formed via direct oxidative addition of radicals to Pd(0), CO insertion and subsequent reductive elimination to afford the amide product, and the Pd(0) species is regenerated to complete the catalytic cycle.



Scheme 26 Huang's aminocarbonylation of methylarenes.



Scheme 27 Dyson's aminocarbonylation of methylarenes.

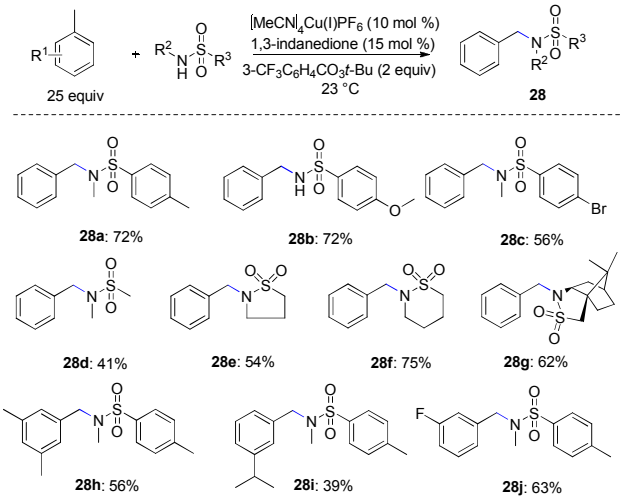
Dyson *et al.* have shown the aminocarbonylation of aromatic amines using $PdCl_2$ and Xantphos catalytic system (Scheme 27).[37] This system works well with anilines having

both the electron withdrawing and donating substituents, although electron withdrawing groups are more favourable. Surprisingly, this catalytic combination is inactive for alkylamines. Sequential oxidation of the in situ generated Pd(0) catalyst by the aniline and benzyl radicals, formed by DTBP, leads to the formation of a benzyl palladium amine species, which undergoes carbonylation with CO and reductive elimination to afford the final product.

3.3 Alkylation reactions.

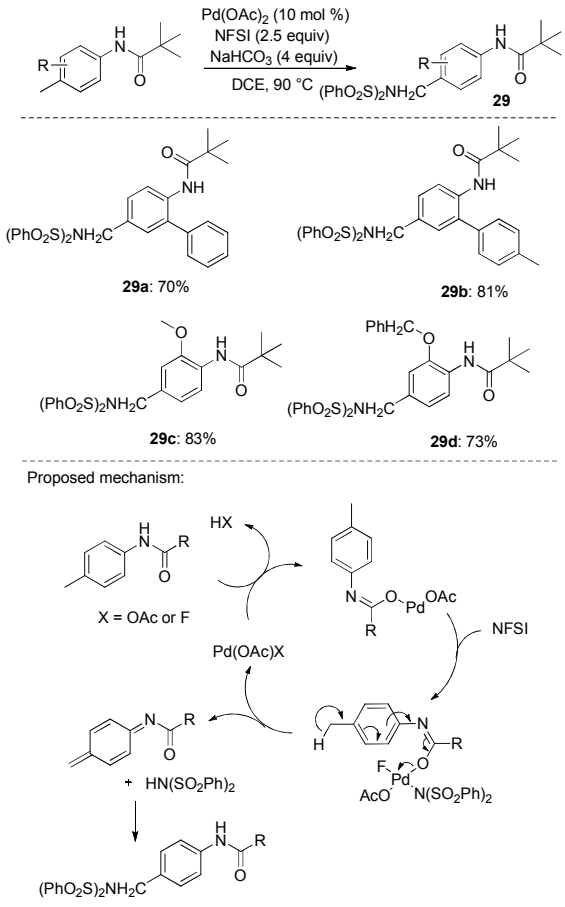
3.3.1 Alkylation of amides or amines.

Early methodologies for the amination of primary benzylic C-H hydrocarbons such as toluene typically afforded low product yields.[38a-c] Notable exceptions included copper- and rhodium-catalyzed nitrene based aminations, although these aminations employed limited primary benzylic substrates.[38d-g] In 2010, Powell *et al.* reported amination of benzylic C-H bonds with sulphonamides with enhanced substrate scope employing $[MeCN]_4Cu(I)PF_6$ as catalyst, 1,3-indanedione as ligand and 3-$CF_3C_6H_4CO_3t$-Bu as oxidant at room temperature (Scheme 28).[39] The reaction is applicable tothe coupling of a number of primary and secondary benzylichydrocarbons with a diverse set of sulfonamides and istolerant of substitution on both the coupling partners. The amination of 3-isopropyltoluene is observed exclusively at the primary benzylic position rather than the tertiary benzylic position.



Scheme 28 Powell's benzylic C-H amination.

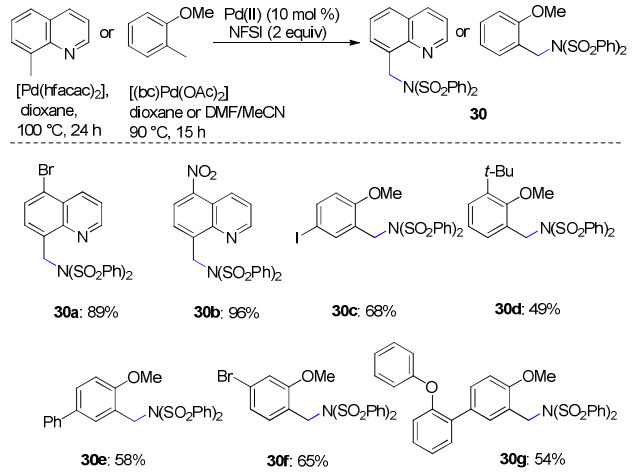
Zhang *et al.* have developed a remote amide directed Pd (II) catalysed highly selective amination of benzylic C-H bond with *N*-fluorobenzenesulfonimide (NFSI) (Scheme 29).[40] *N-p*-Tolylpivalamide is more effective in comparison to other amide directing groups. Reaction scope is limited. Authors believe that the formation of iminoquinone methide intermediate is responsible for the reaction to occur.



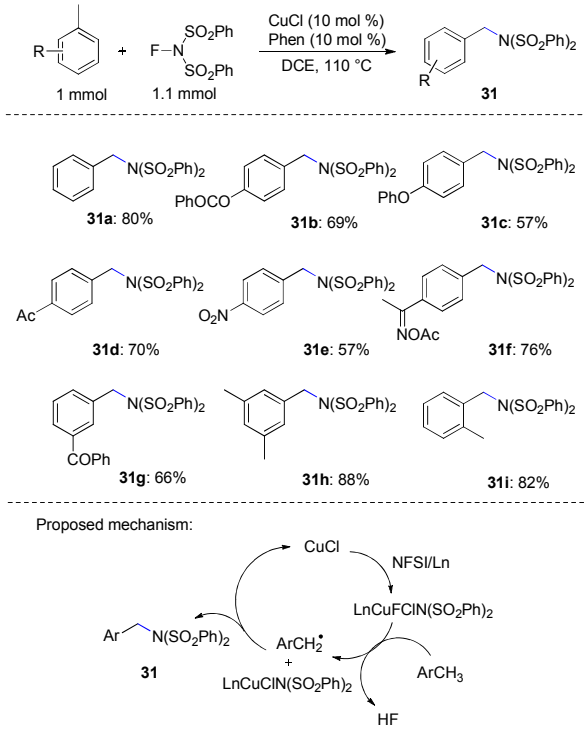
Scheme 29 Zhang's remote benzylic amination.

In 2011, Chen and Qiu reported direct C-N coupling between imidazoles and benzylic hydrocarbons via inexpensive Fe (II)-catalyzed oxidative activation of C-H bonds.[41] In the same year, Cho and Chang described an intermolecular oxidative C-H imidation of arenes with sulfimides using $PhI(OAc)_2$ as an oxidant under metal-free conditions.[42] In 2012, Álvarez and Muñiz developed Pd(II) catalysed amidation of 8-methylquinoline and 2-methylphenyl ethers using NFSI as the key reagent (Scheme 30).[43] For 8-methylquinoline derivatives, $[Pd(hfacac)_2]$ was found to be optimal catalyst, whereas bathocuproine palladium complex $[(bc)Pd(OAc)_2]$ serves as the best catalyst for 2-methylphenyl ethers. The reaction works well for all kinds of 2-methylanisoles bearing *para*, *meta*, and *ortho* substituents on the arene ring.

Zhang and Liu have carried out a highly regioselective benzylic C-H amination by NFSI using CuCl (10 mol %) and 1,10-phenonthroline (10 mol %) (Scheme 31).[44] A broad range of methylarenes were tolerated in the reaction. Polymethylated arenes interestingly afford monoaminated product, however diamination also occurs by increasing the amount of NFSI to 5 equiv. The catalytic system also shows selectivity toward primary benzylic over secondary benzylic position. The plausible mechanism proposed by the authors involves a catalytic cycle involving Cu^{I}, Cu^{II}, and Cu^{III} species.

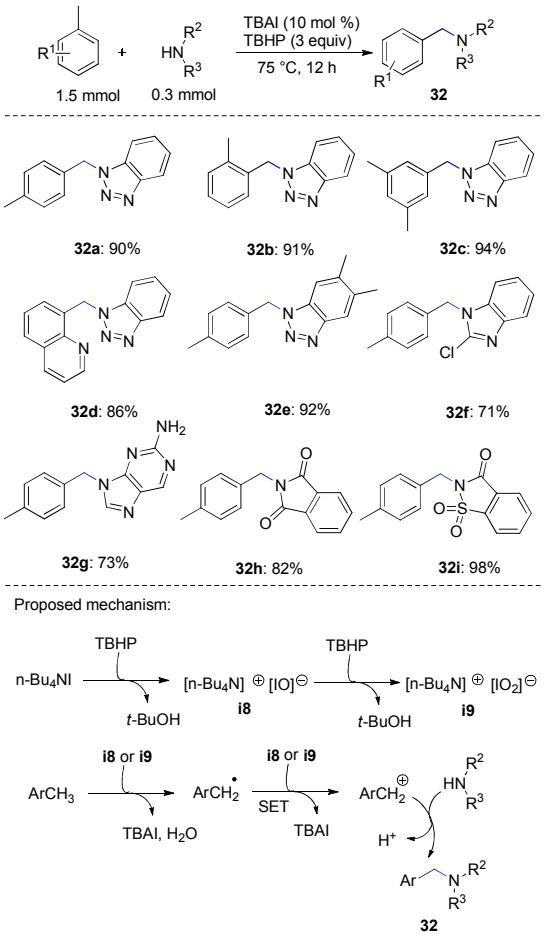


Scheme 30 Álvarez and Muñiz's benzylic C-H amination.



Scheme 31 Zhang and Liu's benzylic C-H amination.

In 2013, Zhu *et al.* exploited the use of TBAI/TBHP catalytic system for amination of benzylic C-H bonds under metal free conditions (Scheme 32).[45a] The conditions tolerate the reaction of a wide range of methylarenes with benzotriazole and benzimidazole derivatives. Radical scavenger such as BHT completely inhibits the reaction and the benzyl radical is trapped by TEMPO. Authors believe that the intermediate $[n\text{-}Bu_4N]^+[IO]^-$ (**i8**) or iodite $[nBu_4N]^+[IO_2]^-$ (**i9**) play an important role in the benzylic C-H amination reaction. These two intermediates are responsible for the generation of benzyl cation, which finally forms the desired product. Later, aryl tetrazoles are also found to participate in the reaction.[45b]



Scheme 32 Zhu's benzylic C-H amination.

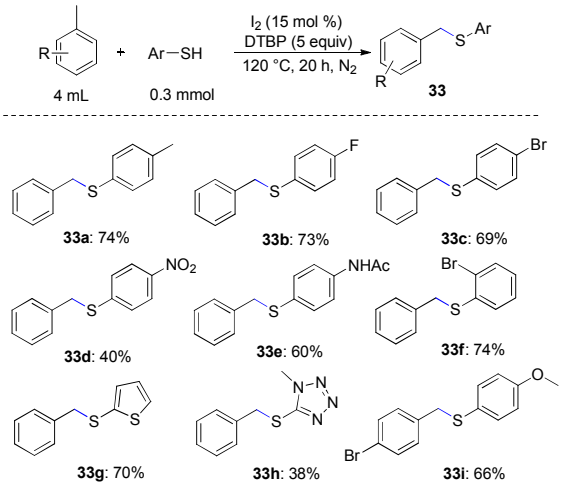
3.3.2 Alkylation of thiophenols.

Lei *et al.* have constructed $C(sp^3)$-S bond from commercially available hydrocarbons and mercaptans using 15 mol % of I_2 and 5 equivalents of DTBP at 120 °C for 20 h under N_2 atmosphere (Scheme 33).[46] The reaction tolerates electron-donating as well as electron-withdrawing substituents on both the coupling partners. Radical scavenger completely inhibits the reaction. Based on control experiments and *in-situ* IR reaction monitoring, the formation of disulphides is implicated in the reaction. Iodine acts as an accelerator for the formation of disulphides, which then react with the benzyl radical.

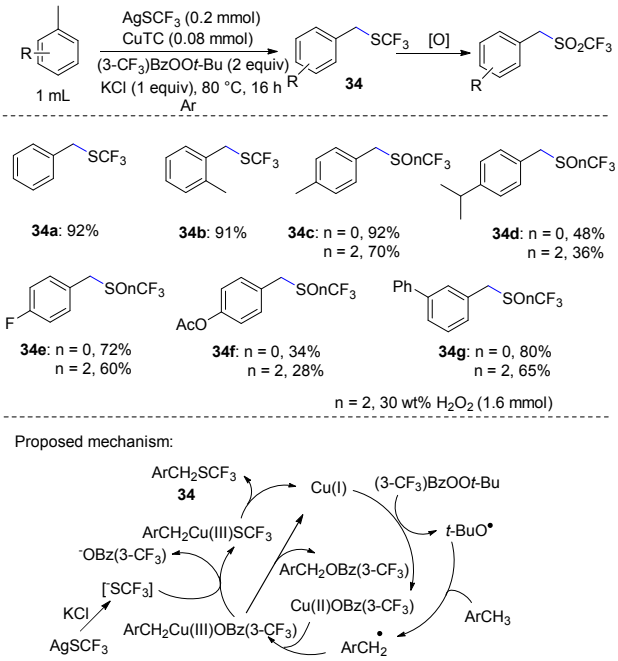
3.3.3 Trifluromethylthiolation

Qing *et al.* have reported a copper-catalysed trifluoromethylthiolation of benzylic C-H bonds using $AgSCF_3$ as trifluoromethylthiol source (Scheme 34).[47] The optimization studies revealed CuTC as the most effective catalyst in presence of (3-CF_3)BzOO*t*-Bu as oxidant and KCl as additive at 80 °C for 16 h under Ar. Various toluene derivatives with different electron-donating or withdrawing substituents at various positions of the aromatic ring were well tolerated. A

plausible mechanism is proposed based on Kharasch-Sosnovsky reaction.



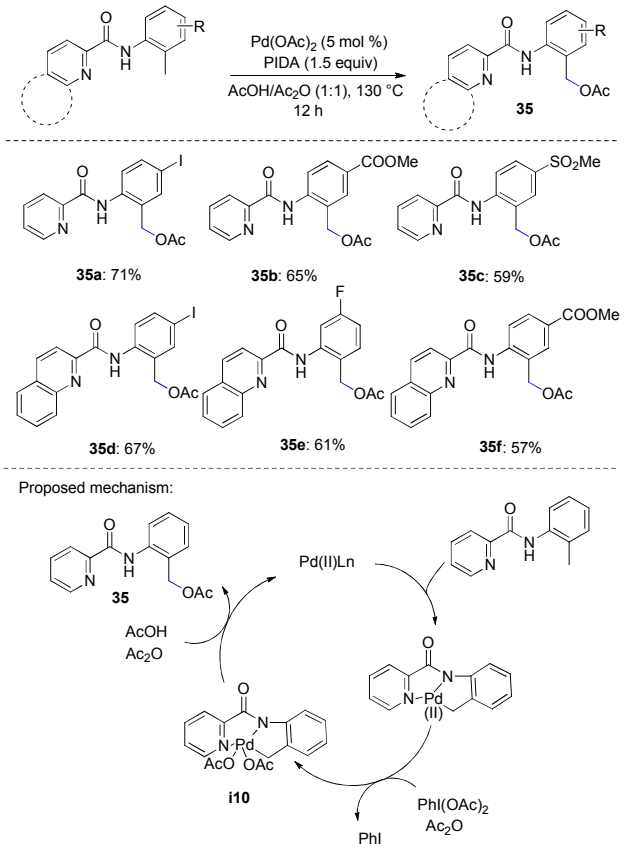
Scheme 33 Lei's alkylation of thiophenols.



Scheme 34. Quing's benzylic C-H trifluoromethylthiolation.

3.3.4 Acetoxylation, fluorination, silylation and arylation/oxidation reactions.

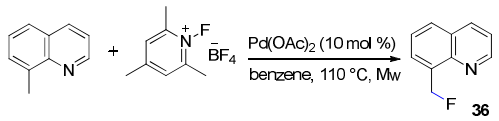
In 2004, Sanford *et al.* reported an early example of Pd(II)-catalyzed acetoxylation of benzylic C–H bonds in quinoline substrates with high levels of chemo- and regio-selectivities.[48] In 2008, Vedernikov *et al.* reported regioselective aerobic oxidation of 5- and 6-substituted 8-methylquinolines in AcOH-Ac_2O solution to produce corresponding 8-quinolylmethyl acetates with Pd(II) complexes derived from 2,6-pyridinedicarboxylic acids.[49] In 2010, Liu and Zhang described $Pd(OAc)_2$-catalyzed oxidative acetoxylation of benzylic C-H bonds utilizing a bidentate auxiliary with $PhI(OAc)_2$ to afford the acetoxylated products (Scheme 35).[50] A broad range of functionalities, such as CH_3, F, Cl, Br, I, $COCH_3$, CO_2Et, SO_2CH_3, and NO_2 present on picolinoyl-protected toluidines as well as quinoline-2-carbonyl-protected toluidine auxiliaries are well tolerated. The plausible mechanism proposed by the authors proceeds via a Pd^{II}/Pd^{IV} pathway. The palladacycle intermediate by the oxidation with $PhI(OAc)_2$ in the presence of Ac_2O and HOAc affords a Pd(IV) center intermediate (**i10**), which undergoes a reductive elimination process to furnish the acetoxylated products as shown in Scheme 35.



Scheme 35 Liu and Zhang's benzylic C-H acetoxylation.

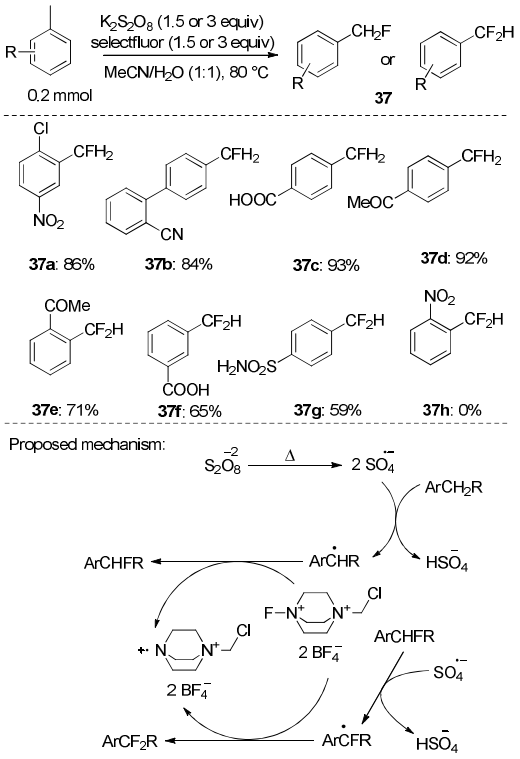
Sanford *et al.* developed a Pd(II)-catalyzed fluorination of benzylic C–H bonds under oxidative conditions using electrophilic *N*-fluoropyridinium reagents. The fluorination of benzylic C–H bonds in substituted 8-methylquinoline derivatives necessitated the use of microwave irradiation (Scheme 36).[51] Chen *et al.* developed an operationally simple benzylic mono- and difluorination using 9-fluorenone and xanthone catalyst respectively under visible light irradiation with selectfluor as fluorine source.[52]

In 2015, Yi *et al.* reported transition metal-free C-H oxidative activation for selective benzylic mono- and



Scheme 36 Sanford's benzylic C-H fluorination.

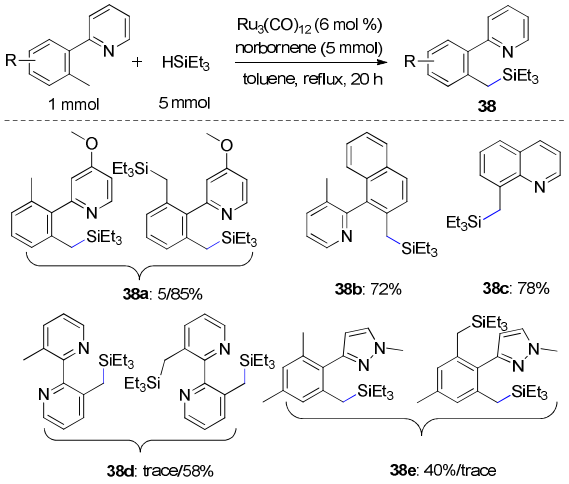
-difluorination using persulfate as promoter and selectfluor as fluorine source (Scheme 37).[53] The best result was achieved by using 1.5 equiv. of selectfluor and 1.5 equiv. of potassium persulfate in MeCN/H_2O (v/v = 1:1) at 80 °C for 4 h. Lowering the temperature and the amount of selectfluor and persulfate lowers the yields. Increasing the amount of selectfluor leads to the difluorination of benzylic C-H bonds. A wide variety of functional groups/substituents such as cyanide, phenyl, *tert*-butyl, ketones, halo, nitro, and carboxylic acid derivatives are tolerated in the reaction. Addition of radical scavengers inhibits the reaction completely. A plausible mechanism based on control experiments is proposed by the authors.



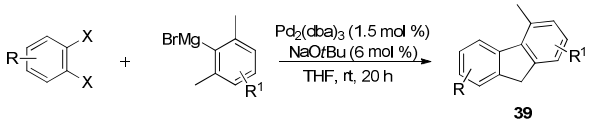
Scheme 37 Yi's benzylic C-H fluorination.

In 2004, Kakiuchi *et al*. introduced $Ru_3(CO)_{12}$ catalysed chelation assisted silylation of benzylic C-H bonds with hydrosilanes (Scheme 38).[54] Triethylsilane in the presence of norbornene was selected as an effective reagent. A series of directing groups were tested in the reaction, among which pyridyl, pyrazolyl, and hydrazones, function effectively.

In 2000, Catellani *et al.* showed a Pd(0)-catalyzed activation of benzylic methyl groups with the formation of cyclopentene ring with norbornene.[55] In 2005, Sanford *et al.* described a Pd(II)-catalyzed direct arylation of benzylic C–H bonds with hypervalent iodine(III) as arylating reagent.[56] In the same year, Daugulis *et al.* reported a Pd(II)-catalyzed arylation of benzylic C–H bonds of quinoline derivatives with aryl iodides.[57] In 2008, Fagnou *et al.* reported Pd(0)-catalyzed site selective arylation reactions of both sp^2 and benzylic sp^3 C–H bonds of azine and diazine *N*-oxide substrates with aryl halides.[58] Hu *et al.* have synthesized fused five membered carbocycles involving the coupling of 1,2-dihalobenzenes with 2,6 dimethylphenylmagnesium reagents (Scheme 39).[59] The reaction proceeds via Pd(0) catalysis involving cross-coupling followed by the oxidative cyclization. A variation of this method, in which the 1,2-dihalobenzene was replaced by an internal alkyne, was also reported by the same group.[60]



Scheme 38 Kakiuchi's benzylic C-H silylation.

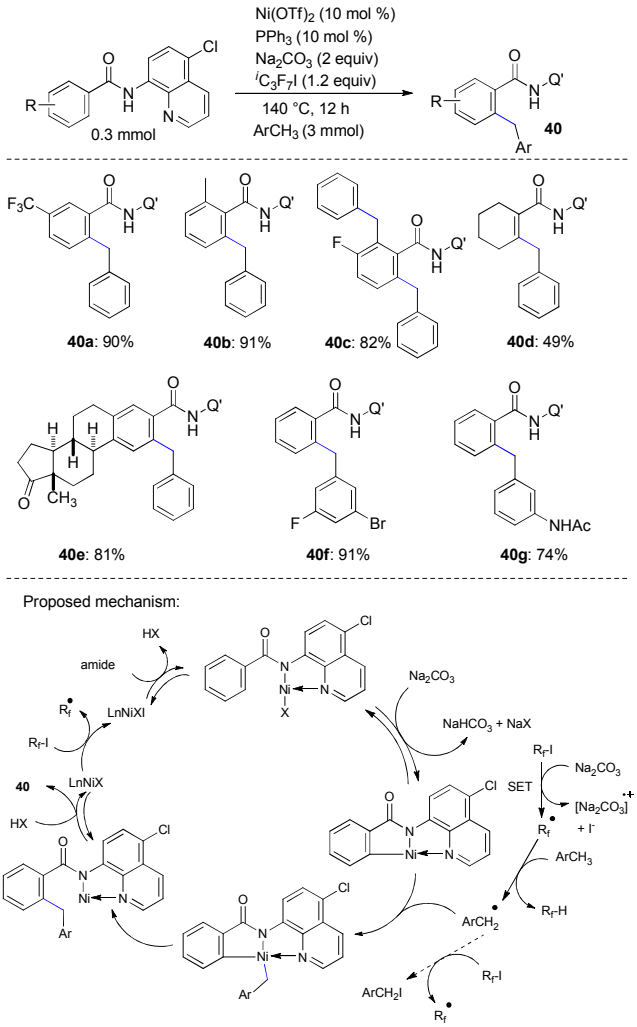


Scheme 39 Hu's oxidative cyclisation.

Chatani *et al.* have reported an interesting oxidative coupling between C(sp^2)-H and C(sp^3)-H bonds by the $Ni(OTf)_2$-catalyzed reaction of benzamides containing 8-aminoquinoline moiety as the directing group with toluene derivatives in the presence of heptafluoroisopropyl iodide as an oxidant (Scheme 40).[61] The method is generally broad in scope and shows high functional group tolerance. In almost all the cases, mono benzylation products are obtained. A plausible mechanism is proposed by the authors based on deuteration and radical scavenging experiments.

Zhang *et al.* have made a proficient use of $Pd(OAc)_2$/AgOAc combination for benzylic C-H arylation/oxidation reaction using amide bidentate directing group with aryliodides leading to diaryl ketones (Scheme 41.)[62] The reaction tolerated a broad range of functional groups, although the *ortho* substituted aryliodides failed to give the products. Analysis of

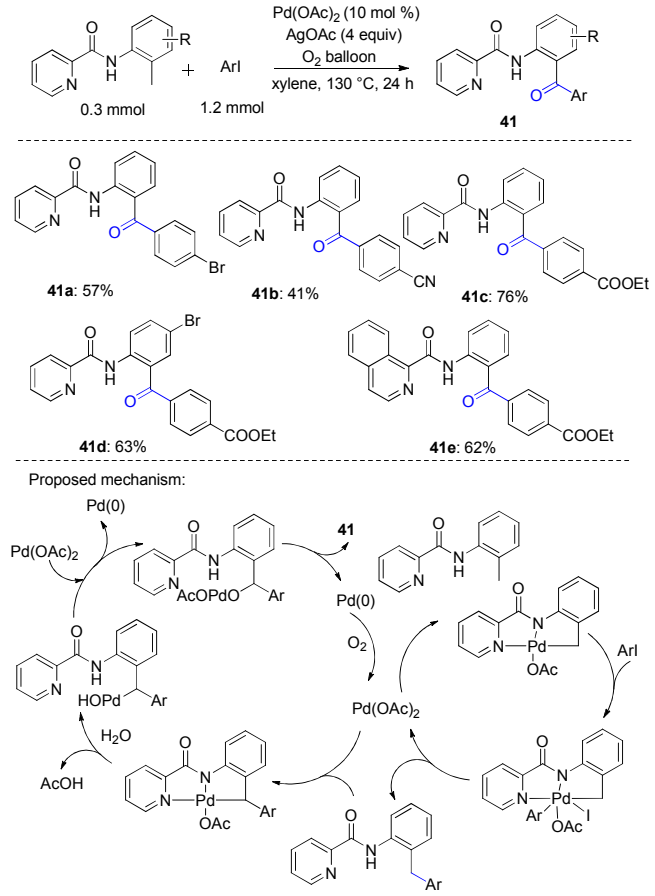
the reaction mixture revealed the formation of arylated product in the reaction mixture and its subsequent oxidation to give the product.



Scheme 40 Chatani' benzylic C-H arylation.

3.3.5 Alkylation of carboxylic acids and alcohols.

In 2011, Zhang and Yu reported the oxidative esterification of benzylic C-H bonds with carboxylic acids using TBAI/TBHP-catalytic system.[63] In 2012, Zhang *et al.* reported benzylation of carboxylic acids with toluene using palladium catalysis under oxygen (Scheme 42).[64] The optimal conditions employed 10 mol % $Pd(OAc)_2$, 1.0 equiv. of DMA and 10 mol % of trifluoromethanesulfonic acid under 1 atm of O_2 in 0.5 mL of toluene at 115 °C for 24 h. Both electron-donating and electron-withdrawing substituents are well tolerated. A plausible mechanism is also proposed by the authors.

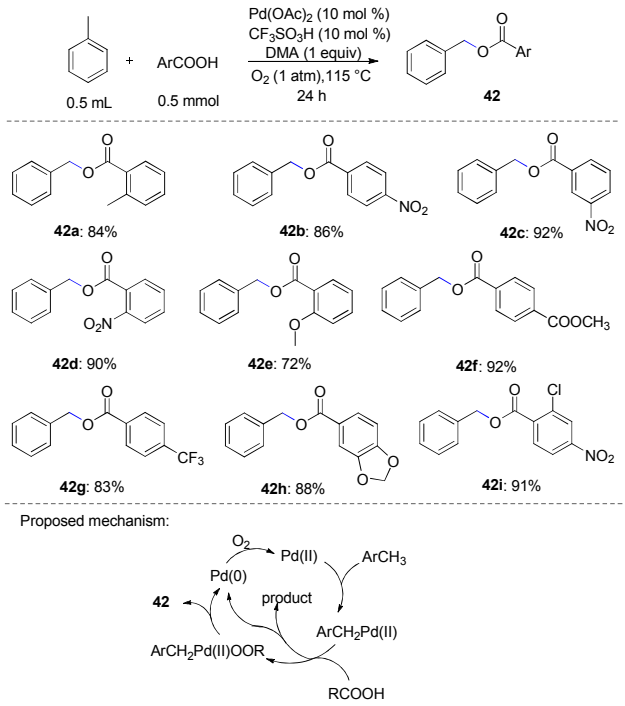


Scheme 41 Zhang's benzylic C-H arylation/oxidation.

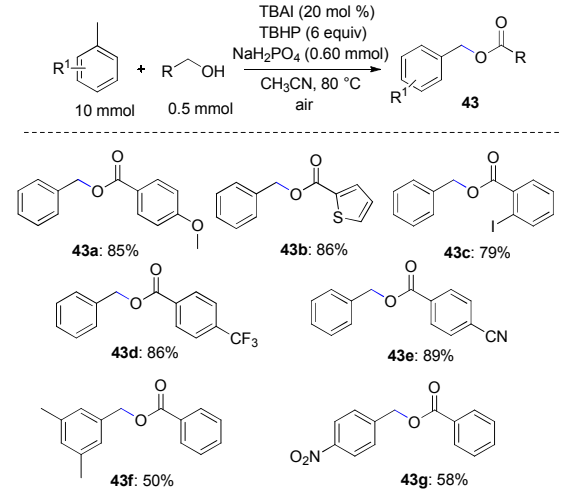
Fu *et al.* made use of TBAI/TBHP catalytic system for the direct esterification of alcohols with different toluene derivatives (Scheme 43).[65] Mechanistic investigations indicate that the alcohols are sequentially oxidized to aldehydes and carboxylic acids, which then react with benzyl iodide generated from methylarene with I_3^-. Reaction scope is broad and tolerance of functional groups is excellent.

3.3.6 Synthesis of phosphate esters.

In 2014, Tang *et al.* reported an interesting phosphorylation of benzylic C-H bonds leading to the synthesis of phosphate esters using 20 mol % of TBAI with 8 equivalents of TBHP at a temperature of 90 °C for 12 h (Scheme 44).[66]. The reaction was tested with different substitutions on methylarenes. Radical scavengers inhibit the reaction; the reaction is also suppressed when I_2 is used instead of Bu_4NI. However, the combined use of I_2 and Bu_4NI leads to 40% yield of the product. The results suggested the involvement of either ammonium hypoiodite **i8** or iodite **i9** catalytic species formed by the reaction between Bu_4NI and TBHP. The benzyl radical formed from toluene is further oxidized to benzyl cation, which couples with $Ph_2P(O)OH$ formed by the oxidation of $Ph_2P(O)H$ by TBAI/TBHP to provide the product in the end.



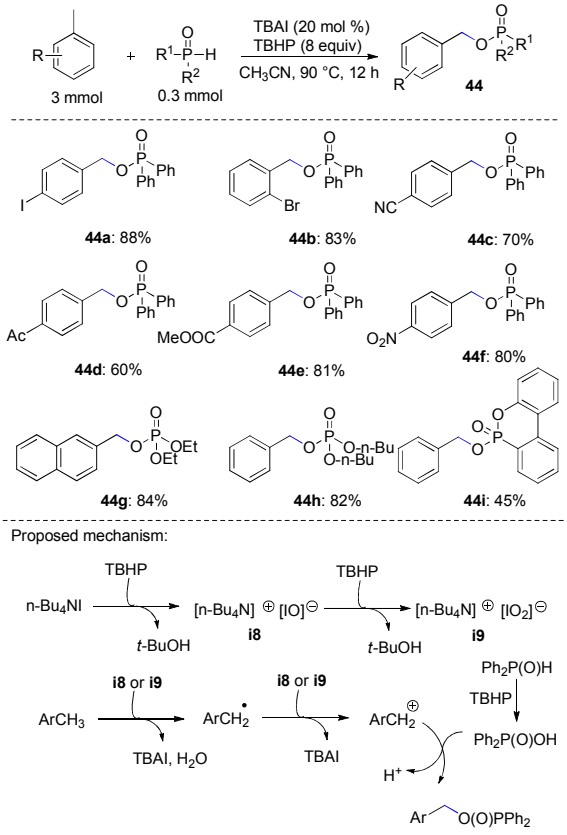
Scheme 42 Zhang's approach for alkylation of carboxylic acids.



Scheme 43 Fu's approach for alkylation of alcohols leading to esters.

3.3.7 Synthesis of carbamates, thioamides and esters.

Our group has reported an efficient utilization of toluene derivatives for the synthesis of carbamates, thioamides, and esters using TBHP/NBS catalytic system (Scheme 45).[67] The strategy depends on the initial conversion of methylarene to benzyl bromide with the help of a radical initiator TBHP (catalytic) and NBS as brominating agent, which is then converted to carbamates, thioamides, and esters by the application of suitable reagents. Reaction showed broad substrate scope and functional group tolerance with good to excellent yields in almost all cases.



Scheme 44 Tang's synthesis of phosphate esters.

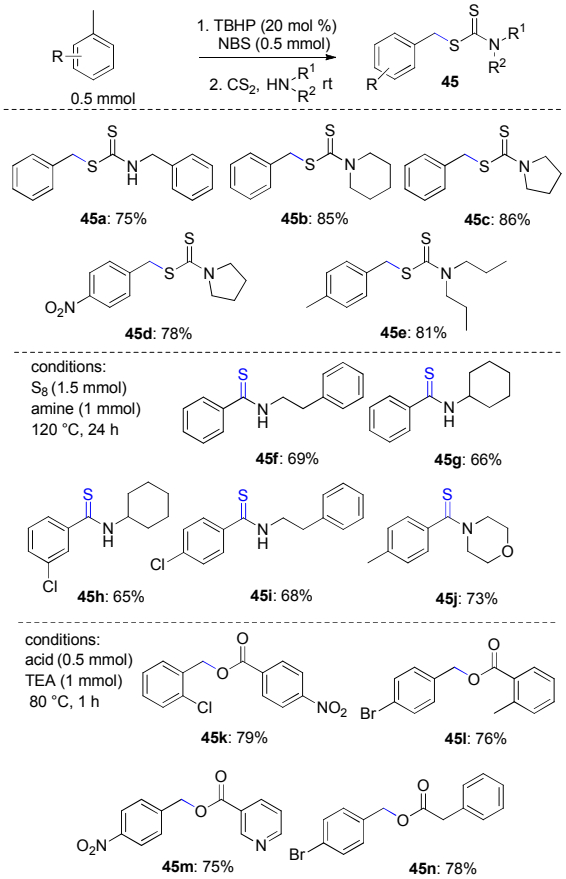
3.3.8 Some other reactions.

In 2006, Chang *et al.* synthesized aryl lactones from *ortho*-alkyl substituted aromatic carboxylic acids primarily using platinum via chelation assistance of carboxylic group (Scheme 46).[68]

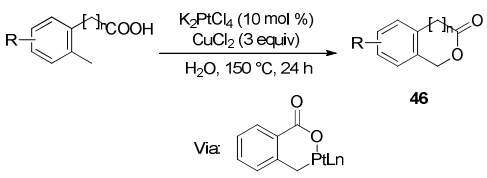
In 2014, Lee *et al.* have described an interesting azaphosphaannulation of *ortho* alkyl substituted phosphonamides through intramolecular oxidative C–N bond formation using $PhI(OAc)_2$ and iodine under air, leading to the formation of benzazaphosphol-3-one 1-oxides (Scheme 47).[69] The reaction shows broad substrate scope leading to the products in high yields. The reaction is sensitive to the substituents on N and P groups of phosphonamides and 2,6-disubstitution is essential. The reaction was quenched by the use of TEMPO, suggesting a radical pathway. The plausible mechanism involves the reaction of $PhI(OAc)_2$ with iodine to provide phenyl iodide and acetyl hypoiodite (AcOI). Phosphonamide on reaction with acetyl hypoiodite affords phosphonamidyl radical, which undergoes 1,5-H shift to give the benzyl radical which on subsequent reaction with iodine and hydrolysis leads to the formation of the product.

Minami and Hiyama have exemplified hydrobenzylation of ortho-tolyl alkynyl ethers using palladium catalysis via benzylic C-H insertion and subsequent *syn*-1,2-addition across the alkyne (Scheme 48).[70] The adducts 2-methylidene-2,3-dihydrobenzofurans easily react with acetic acid, azo and carbonyl compounds, and molecular oxygen to give various functionalized benzofurans.A variety of aryl

triisopropylsilylethynyl ethers were used for the hydrobenzylation. In almost all cases, yields were excellent. A plausible mechanism as proposed by the authors is shown in Scheme 48.

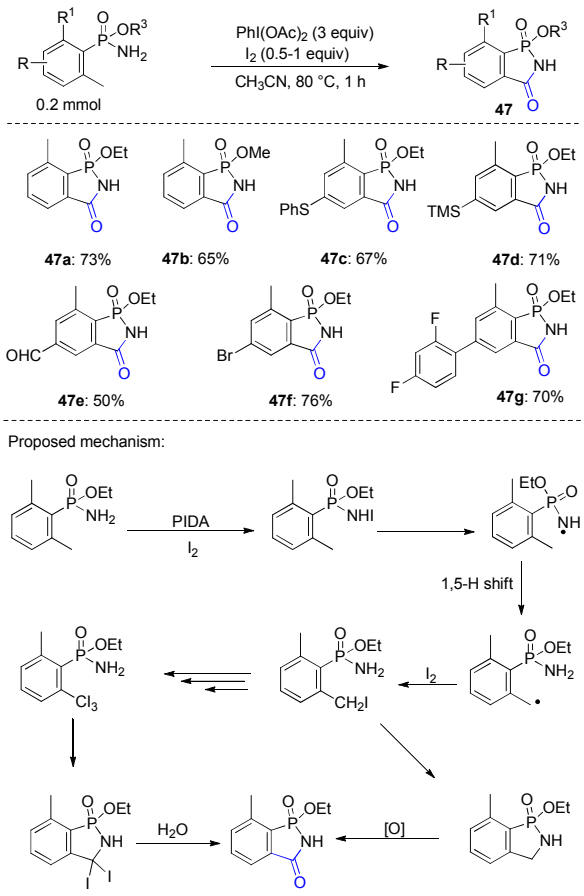


Scheme 45 Singh's approach for synthesis of carbamates, thioamides and esters.

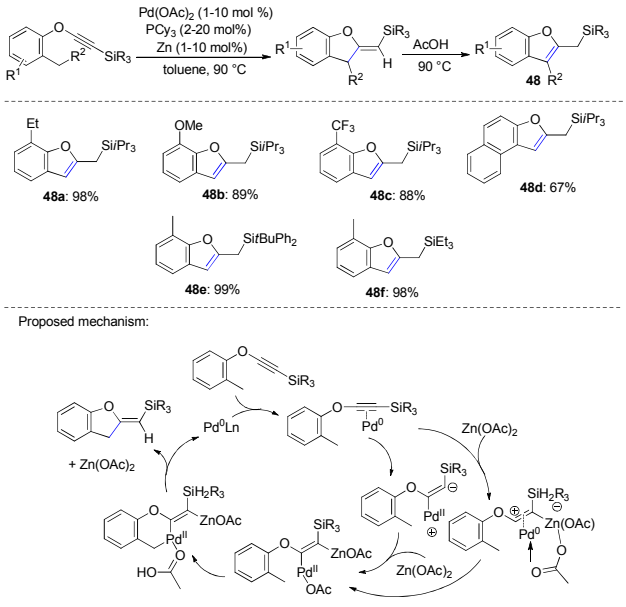


Scheme 46 Chang's synthesis of lactones.

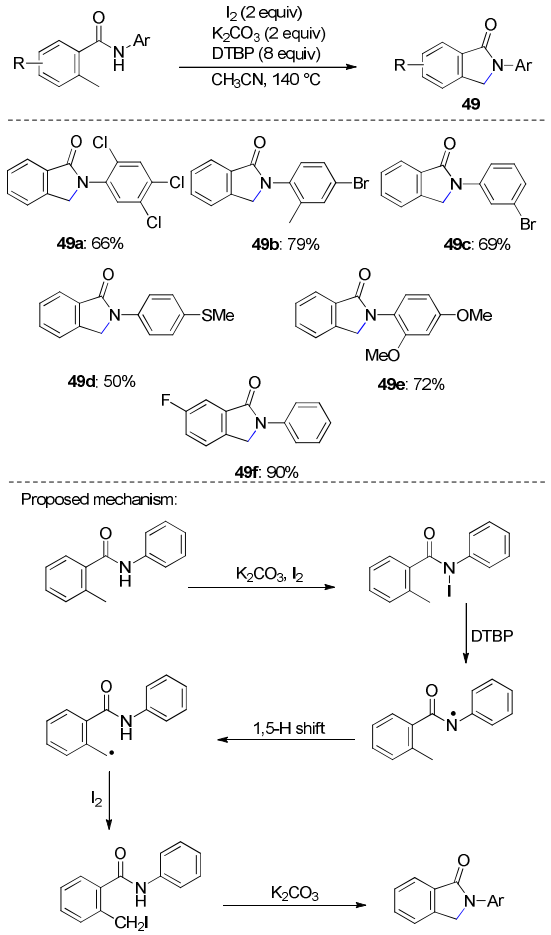
Kumar *et al.* have illustrated the synthesis of *N*-arylisoindolinones through intramolecular oxidative C–N bond formation of *ortho*-alkyl benzamides using I_2 and DTBP system (Scheme 49).[71] The reaction shows good compatibility with different functional groups to afford products in good yields. A plausible mechanism proposed by the authors, shows the involvement of nitrogen centre radical which undergoes 1,5-H shift to give benzyl radical, which upon further reaction with I_2 and base undergoes cyclization to give the product.



Scheme 47 Lee's approach for azaphosphaannulation.



Scheme 48 Minami and Hiyama's approach for hydrobenzylation.

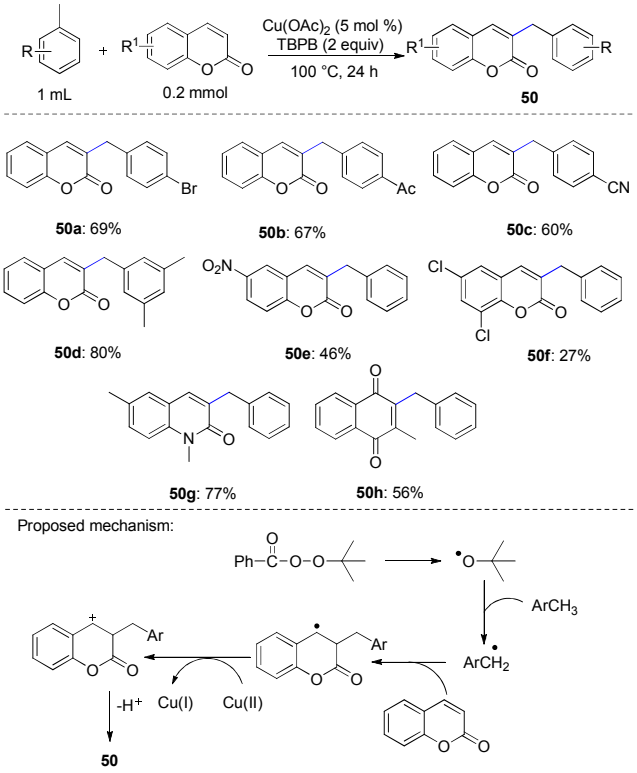


Scheme 49 Kumar's approach for N-arylisoindolinones.

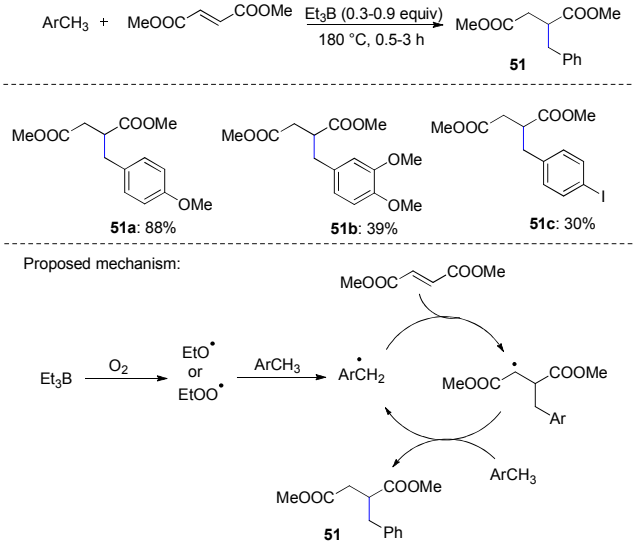
Duan *et al.* have reported a regioselective coupling of methylarenes with coumarins using $Cu(OAc)_2$ and *t*-butylperoxy benzoate (TBPB) (Scheme 50).[72] The reaction is applicable to both electron-withdrawing and electron-donating substituted methylarenes with good functional group tolerance. Radical scavengers inhibit the reaction completely and the authors propose a mechanism involving benzyl radical which reacts with coumarin derivatives to give the product.

Miyata *et al.* have reported the benzyl radical addition to electron deficient alkenes in the presence of Et_3B as a radical initiator (Scheme 51).[73] The benzyl radical is generated in the presence of Et_3B and oxygen, and then reacts with the alkene to give a radical intermediate, which abstracts a hydrogen radical from another toluene molecule to give the product.

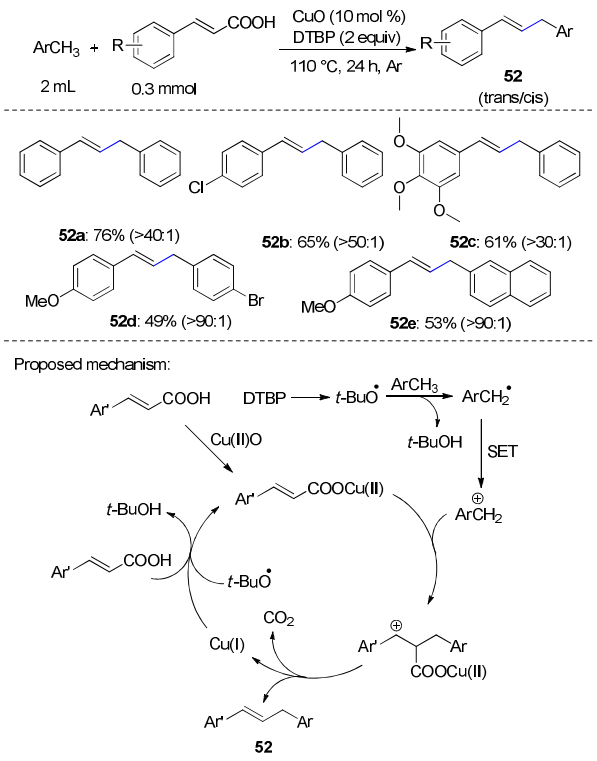
Mao *et al.* have illustrated a decarboxylative coupling of methylarenes with cinnamic acids using CuO and DTBP catalytic system (Scheme 52).[74] The reaction tolerates both the electron-withdrawing and electron-donating substituents on both the coupling partners except 4-nitrocinnamic acid. The plausible mechanism proposed by the authors generates benzyl cation via DTBP activation and SET process assisted by Cu(II) catalyst. Benzyl cation undergoes reaction with cupric cinnamate, generated from cinnamic acid and CuO, followed by decarboxylation to provide the product. The same group later reported an iron catalysed version of the reaction.[75] Song *et al.* reported another variation of the reaction starting from aldehydes via *in-situ* generated cinnamic acids using copper and DTBP catalysis.[76]



Scheme 50 Duan's approach for regio selective coupling of methylarenes with coumarins.



Scheme 51 Miyata's approach for radical benzylic addition.

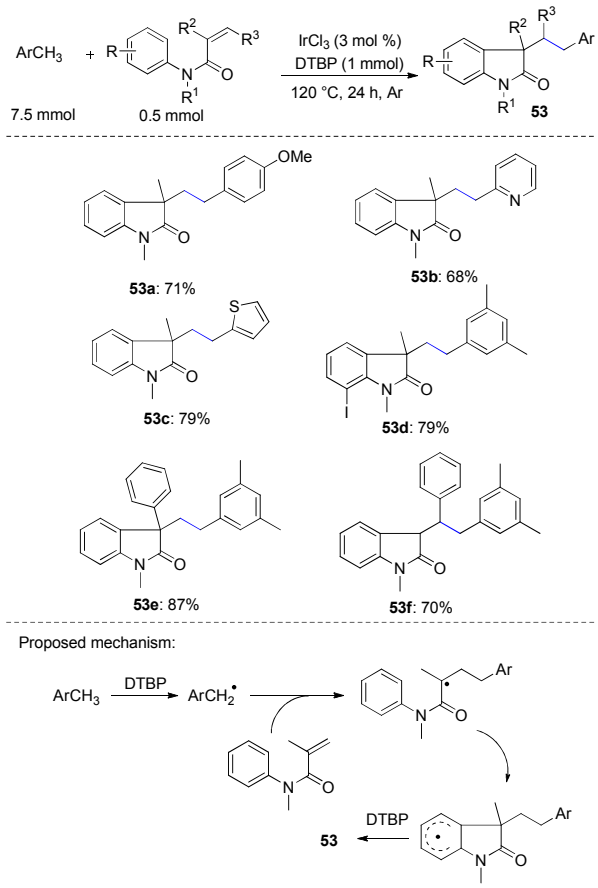


Scheme 52 Mao's approach for decarboxylative coupling.

Li *et al.* have achieved the synthesis of functionalised oxindoles from methylarenes and acrylamides using $IrCl_3$ and DTBP (Scheme 53).[77] Several substituents on both the coupling partners participated in the reaction; polymethylated arenes selectively participate in the reaction. The possible mechanism proposed by the authors passes through the benzyl radical which undergoes cyclisation with the amide partner to form the product. Simultaneously Guo and Duan reported a copper (Cu_2O) catalysed approach for the synthesis of oxindoles with broader substrate scope using TBPB (*tert*-butylperoxy benzoate) as radical initiator.[78] Liu *et al.* also studied the reaction in the midst of Cu_2O and DCP (dicumyl peroxide) catalytic system.[79]

Duan *et al.* have developed a copper catalysed tandem oxidative cylclisation of cinnamides with methylarenes to afford dihydroquinolinones (Scheme 54).[80] The catalytic system Cu_2O and TBPB (*tert*-butyl peroxybenzoate) effectively worked for various substituted reactants. The possible mechanism proceeds through the benzyl radical, which adds to the double bond of the cinnamide, and eventually undergoes cyclisation via single electron transfer mechanism.

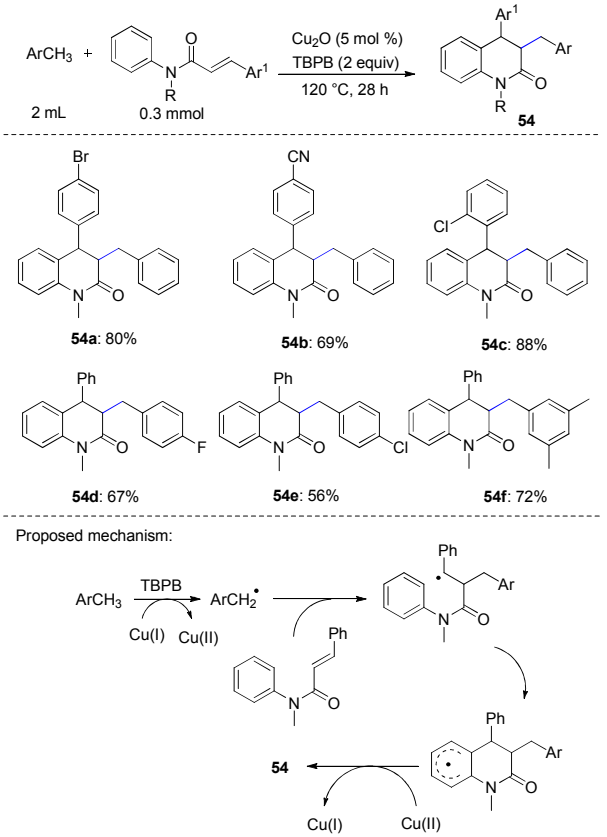
The group of Huang has developed a copper-catalyzed, regioselective α-benzylation of enones with methylarenes under oxidative conditions (Scheme 55).[81] The optimal conditions utilize $Cu(tfacac)_2$ (5 mol %), DTBP (2 equiv), and salicylic acid (20 mol %) at 120 °C for 24 h. Both the electron-rich and electron-deficient aromatic enones along with various substituted methylarenes are effectively used in the reaction. Radical scavengers inhibit the reaction. Based on control experiments the authors propose a mechanism involving generation of benzyl radical from toluene. The benzyl radical adds to the substrate providing radical intermediate **i11**, which can be oxidized by Cu(II) to form the cationic intermediate **i12**. Finally, the intermediate **i12** is deprotonated by the basic *t*-BuO^- to give the desired product. Reoxidation of Cu(I) to Cu(II) by another molecule of alkoxy radical facilitates the catalytic cycle.



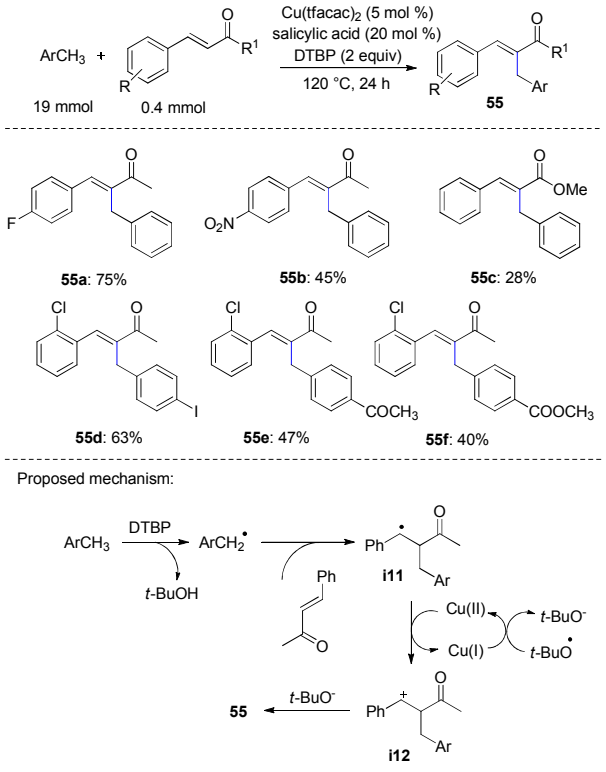
Scheme 53 Li's approach for oxindoles.

Li *et al.* reported an iron-catalyzed oxidative C-C bond formation by the reaction of simple toluene derivatives with 1,3-dicarbonyl compounds (Scheme 56).[82] The combination of $Fe(OAc)_2$ and DTBP was successfully used for several substituted methylarenes. The proposed mechanism again proceeds through the formation of benzyl radical.

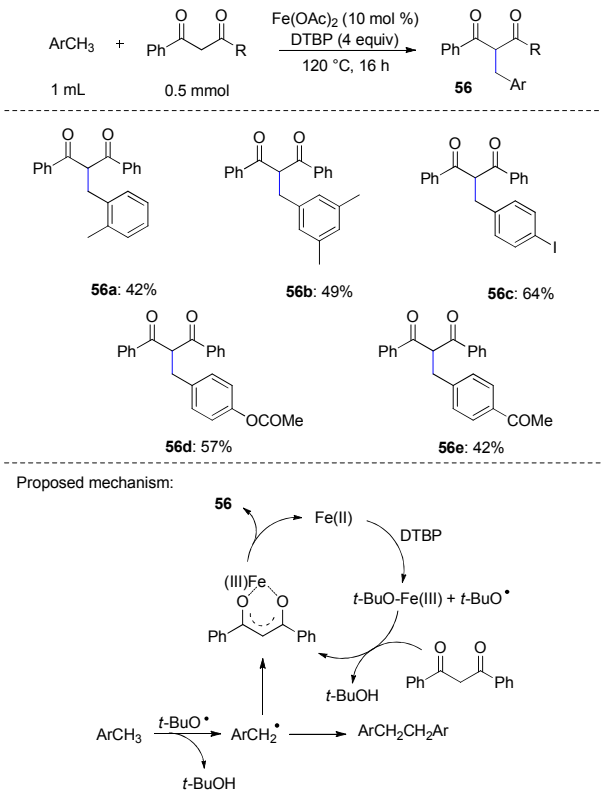
In an interesting protocol, Song *et al.* have reported the formation of $C(sp^3)$-$C(sp^2)$ and $C(sp^3)$-$C(sp^3)$ bonds in a single operation using 1,3-dicarbonyl compounds and methylarenes (Scheme 57).[83] The reaction was achieved in the presence of $FeCl_2$ and DDQ in DCE. Mechanistic studies suggest the role of Friedel-Crafts type alkylation followed by cross dehydrogenative coupling. The reaction proceeds with the formation of benzyl cation by the action of $FeCl_2$ and DDQ, which undergoes Friedel-Crafts type alkylation with another molecule of arene to generate a new benzylic compound,



Scheme 54 Duan's approach for dihydroquinolinones.



Scheme 55 Huang's approach for regio selective α-benzylation of enones



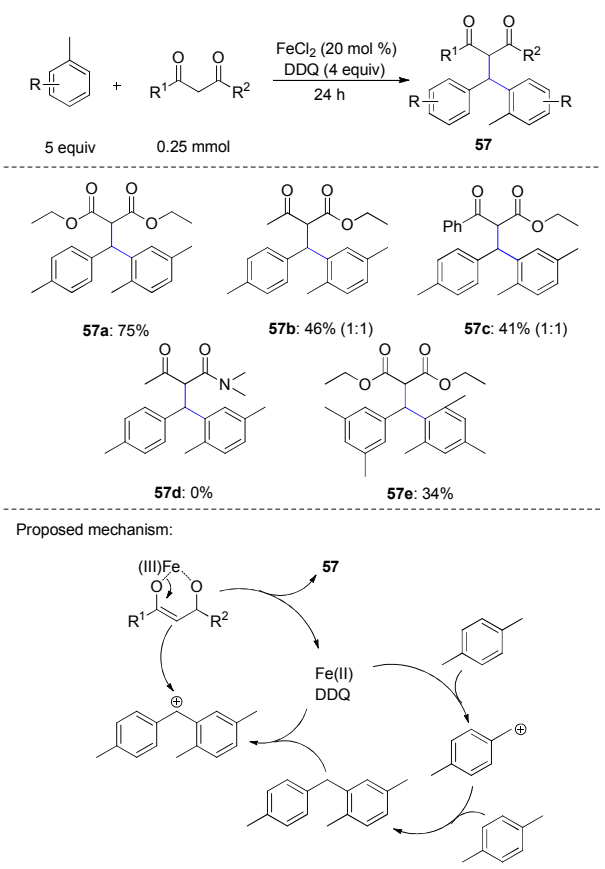
Scheme 56. Li's approach for benzylation of 1,3-dicarbonyl compounds

which after successive SET process and reaction with 1,3-dicarbonyl compound gives the product.

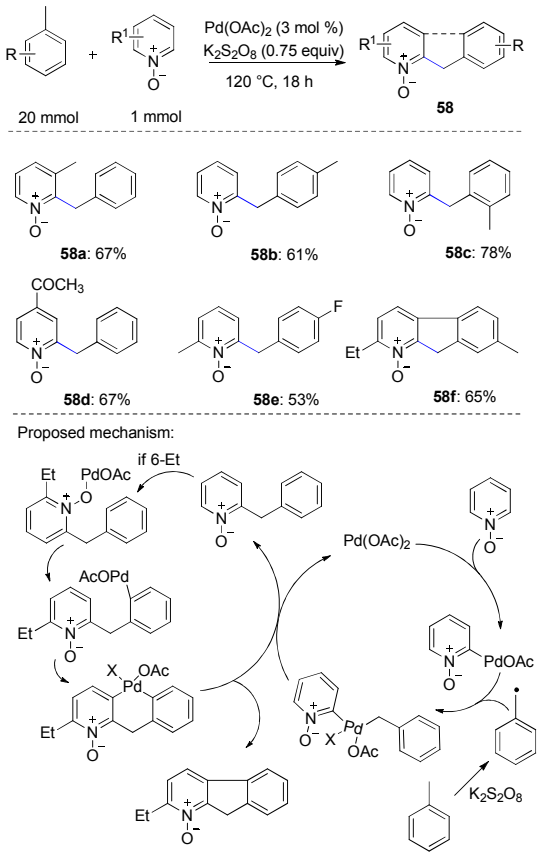
Kianmehr *et al.* reported an interesting palladium catalysed regioselective benzylation of pyridine *N*-oxides with methylarenes in the presence of $Pd(OAc)_2$ and $K_2S_2O_8$ at 120 °C for 18 h (Scheme 58).[84] When use was made of $Cu(OAc)_2$ and TBHP along with $Pd(OAc)_2$, mono arylation could be achieved. Pyridine *N*-oxides containing both the electron-donating and electron-withdrawing groups react smoothly and result in the corresponding 2-benzylpyridine *N*-oxides. When 2-ethylpyridine *N*-oxide is used as a substrate, the reaction leads to the formation of the azafluorene *N*-oxide derivatives. A possible mechanism is also proposed by the authors.

Kozlowski *et al.* have disclosed an interesting coupling of sp^2 C-H bond of azlactone and sp^3 C-H bond of methylarene using palladium catalysis (Scheme 59).[85] The plausible mechanism reveals the intermediacy of an azlactone dimer, and is consistent with a Pd-catalyzed C–H activation *vs* a radical process. The formation of benzylic Pd(II) species is proposed which undergoes metathesis with azlactone dimer (path a or c). Another possibility (path b) involves the formation of Pd(IV) intermediate by the oxidative addition of the labile C–C bond of the azlactone dimer to benzylic Pd(II) species, which gives the product on reductive elimination.

Guo *et al.* have carried out an iron-catalyzed tandem oxidative cyclization of olefinic 1,3-dicarbonyl compounds with benzylic C(sp^3)-H bonds, leading to a wide variety of



Scheme 57 Song's approach for coupling of arylmethanes with 1,3-dicarbonyls (the ratio of the two diastereomers was given in the parentheses).



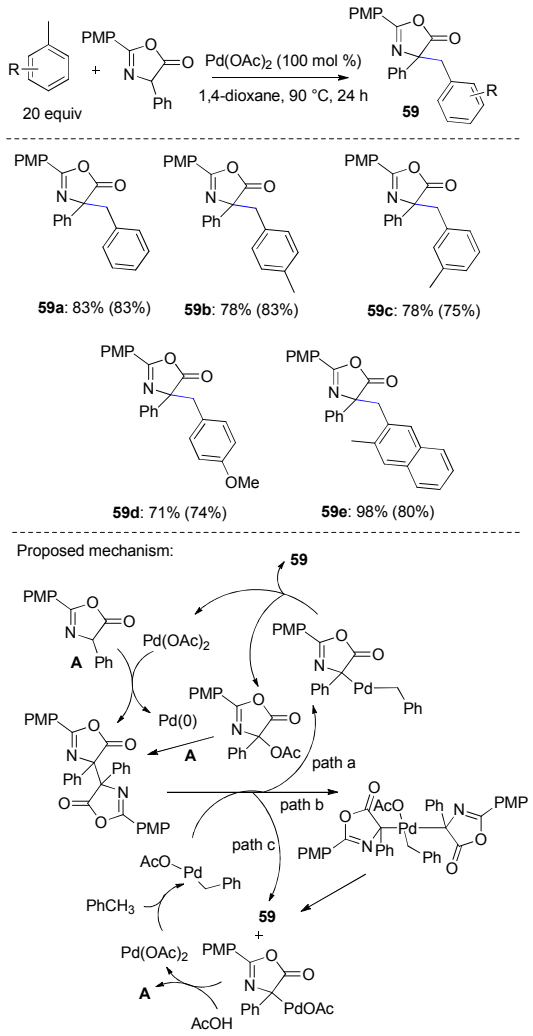
Scheme 58 Kianmehr's approach for benzylation of pyridine-N-oxides.

dihydrofurans containing quaternary carbon centre (Scheme 60).[86] The reaction is achieved by using $FeCl_2$ and TBPB combination. A wide range of methylarenes and olefinic 1,3-dicarbonyl compounds participate in the reaction. The addition of radical scavengers inhibited the reaction, pointing to a radical pathway. Benzyl radical, generated by the action of iron and TBPB, adds across the C=C bond of carbonyl compound followed by cyclization to give the product **60**.

Liu and Wang have reported the preparation of substituted quinolines from *o*-nitrotoluenes and olefins using cesium carbonate (Scheme 61).[87] A variety of substituted *o*-nitrotoluenes with electron-withdrawing groups were found to be efficient substrates. However, substrates without an electron-withdrawing group on the arene ring do not participate in the reaction. Based on control experiments, authors have suggested a one-step mechanism involving [2+4] cycloaddition of nitronate to olefin.

The direct halogenation of alpha C-H of alkylarenes is an important and widely used industrial reaction for the synthesis of bulk and fine chemicals. The selective halogenation of the alpha C-H of alkylarene is often performed by the use of bromine/chlorine gas, and/or *N*-halosuccinimide as halogenating agent. Although an exhaustive literature is available on the synthesis of benzylhalides, only some vital and recent contributions have been covered up.

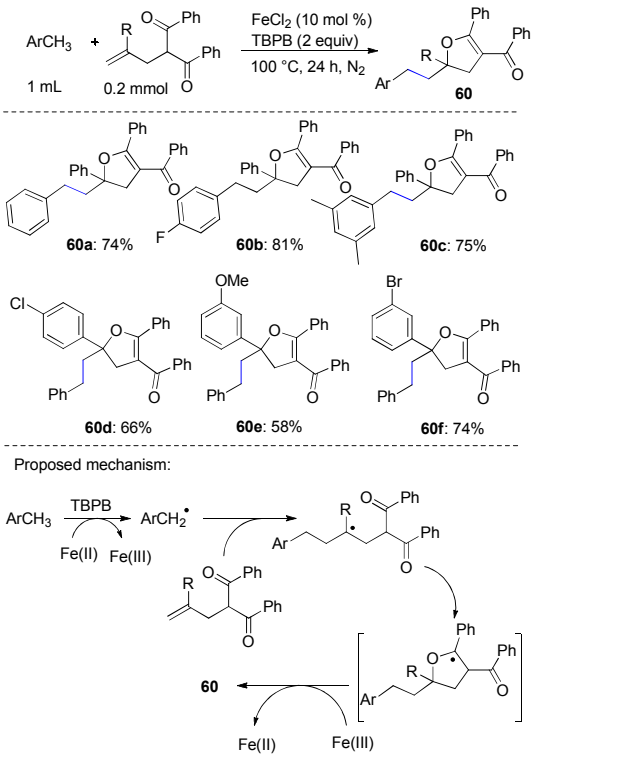
Benzylic bromination constitutes an important class of transformations, as the resulting brominated derivatives are useful and versatile intermediates in organic synthesis. The classical Wohl–Ziegler bromination using *N*-bromosuccinimide (NBS) in refluxing CCl_4 in the presence of a radical initiator such as AIBN (2,2'-azobis(isobutyronitrile)) or BPO has been traditionally used for the purpose.[88] However, in view of emergence of green and sustainable chemistry, several bromination protocols using non-chlorinated solvents appeared. Koten *et al.* have described light-induced or microwave-assisted α-bromination of alkylarenes by NBS using MeOAc as solvent.[89] Salama *et al.* reported halogenation of alkylarenes by *N*-halosuccinimide and tetrachlorosilane in acetonitrile.[90] Iskara *et al.* showed bromination of alkylarenes with NBS in pure water using a 40 W incandescent light-bulb as a radical initiator.[91] Togo *et al.* have achieved bromination of alkylarenes in ionic-liquid under solvent-free conditions to produce the corresponding benzylic bromides.[92] Jereb *et al.* reported visible-light-induced transformation of toluene into benzyl bromide with NBS under solvent-free conditions.[93] Another important aspect involves the use of alternative brominating agents. Mestres *et al.* have employed a two-phase mixture of sodium bromide and aq. H_2O_2 (hydrogen peroxide)/CCl_4 or $CHCl_3$ under visible light, as an alternative agent for benzylic bromination of alkylarens.[94] An aqueous solution of hydrogen peroxide and hydrogen bromide



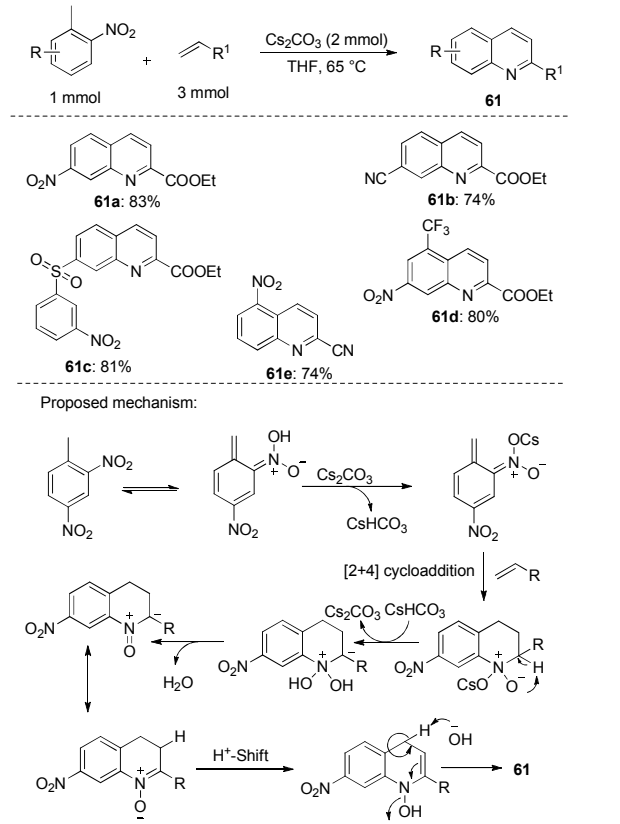
Scheme 59 Kozlowski's approach for Csp^2-Csp^3 coupling of azlactone and methylarenes (the values in parentheses stand for neat reaction).

illuminated by a 40 W incandescent light bulb has also served as a source of bromine radicals to brominate various substituted alkylarenes at the benzylic position.[95] Another report makes use of 2:1 mole ratio of NaBr:$NaBrO_3$ to brominate alkylarenes; the active agent is HOBr generated by the acidification of the reagent mixture.[96] Trichloromethane sulfonylbromide,[97] and bromotrichloromethane,[98] have also been used for effecting the bromination of benzylic C-H bonds. Li *et al.* have made use of bromine in the presence of MnO_2.[99] Another development involves utilisation of different activation methods instead of peroxide radical initiators. Shaw *et al.* showed visible light induced bromination of alkylarenes in the presence of bromine.[100] The group of Mateos and Kappe has developed a continuous-flow protocol for the bromination of benzylic compounds with NBS; the radical reactions are initiated with household compact fluorescent lamp (CFL).[101]

The group of Liu and Whiting has recently reported a visible light induced chlorination of toluene using NaCl/HCl combination as chlorinating agent in the presence of nano-Ag loaded onto the surface of AgCl.[102] Chlorination of toluene is



Scheme 60 Guo's approach for dihydrofuran synthesis.



Scheme 61 Liu and Wang's approach for quinoline synthesis.

also reported by $PhICl_2$ ((dichloroiodo)benzene),[103] SO_2Cl_2,[104] NaOCl,[105] *t*-BuOCl (*t*-butyl hypochlorite),[106] trichloromethanesulfonyl chloride,[107] PCl_5,[108] and trichloroisocyanuric acid,[109] as chlorinating agents.

An early report on benzylic iodination of toluene made an elegant use of *t*-BuOCl/HgI_2.[110] The group of Barluenga has later developed the iodination of toluene by using hypervalent iodine and I_2 combination.[111] Wirth *et al.* reported iodination of hydrocarbons by using *tert*-butyl hypoiodite, generated by the reaction of iodine and sodium *tert*-butoxide.[112] Recently Xiong *et al.* have reported the halogenation utilising CuI/CuBr and TBHP system via *in situ* generation of *tert*-butyl hypoiodite.[113]

Benzylic fluorination was earlier achieved by the use of cesium fluoroxysulfate as fluorinating agent.[114] Recently Tang *et al.* have reported silver-catalyzed difluoromethylation of benzylic C-H of several substituted alkylarenes using selectfluor as fluorinating agent.[115] The group of Lectka has shown photocatalytic fluorination of benzylic C-H by 1,2,4,5-tetracyanobenzene (TCB) in the presence of selectfluor.[116] Chen *et al.* have realized visible light promoted fluorination of benzylic C-H in the presence of diarylketone catalyst and selectfluor as fluorinating source.[117]

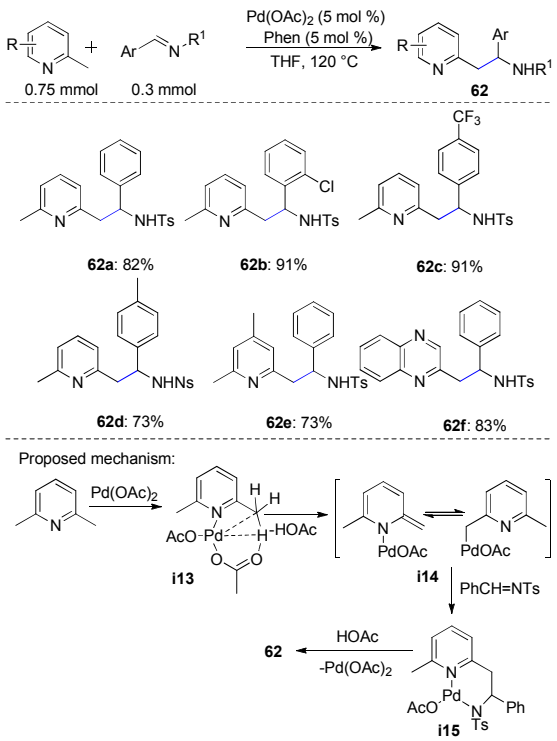
3.4 Reactions of methylazaarenes.

Methylazaarenes have been recognized as a powerful building block mostly in the form of nucleophilic coupling partner to construct diverse useful organic compounds. Based on the nature of involvement of methyl group of methylazarene, the reports have been classified into the following categories.

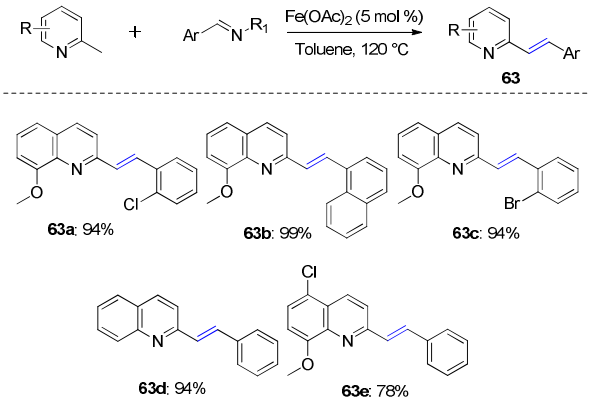
3.4.1 Addition to C=N bond.

In 2010, Xia and Huang developed an efficient and atom-economical protocol for the direct benzylic addition of 2-methyl azaarenes to *N*-sulfonyl aldimines via sp^3 C-H activation in the presence of $Pd(OAc)_2$ and 1,10-phenanthroline under neutral conditions (Scheme 62).[118] Several substituted *N*-tosyl aldimines are effectively used in the transformation. However, when the substrates containing electron-donating substituents on phenyl ring are employed, yields of products are less than 50%. The problem was addressed by the use of *p*-nitrobenzenesulfonyl (Ns) instead of tosyl as the *N*-protecting group. A plausible mechanism as proposed by the authors is also shown in Scheme 62. The substrate coordinates initially with $Pd(OAc)_2$ to form the intermediates **i13** and **i14,** which on subsequent addition to the imine provides intermediate **i15**, which finally gives the product via protolysis and regeneration of the catalyst. The same group also described the $Sc(OTf)_3$-catalysed version of the reaction and extended it for the synthesis of isoindolinones and isoindolines.[119] Later, Rueping *et al.* reported a copper catalysed protocol for the direct benzylic addition of 2-methyl azaarenes to *N*-sulfonyl aldimines.[120]

Huang *et al.* demonstrated an interesting iron-catalyzed approach for alkenylation of 2-substituted azaarenes with *N*-sulfonyl imines using $Fe(OAc)_2$ as catalyst at 120 °C (Scheme 63).[121] Several substituted aldimines as well as quinolines/pyridines containing electron rich and electron poor substituents were effectively used in the transformation. Wang *et al*. reported an operationally simple catalyst-free approach for alkenylation of 2-substituted azaarenes in toluene.[122]

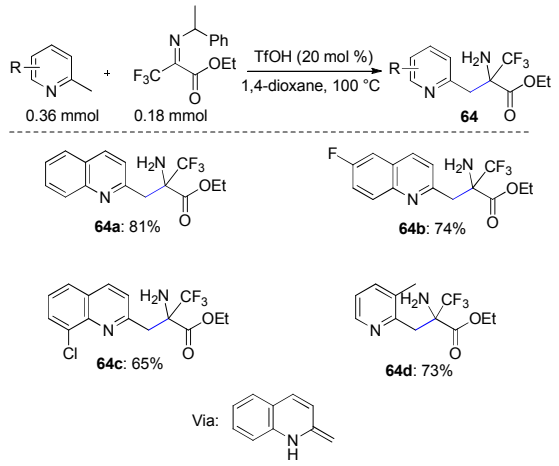


Scheme 62 Xia and Huang's approach for addition of methylazarenes to aldimines.



Scheme 63 Huang's approach for alkenylation of azaarenes.

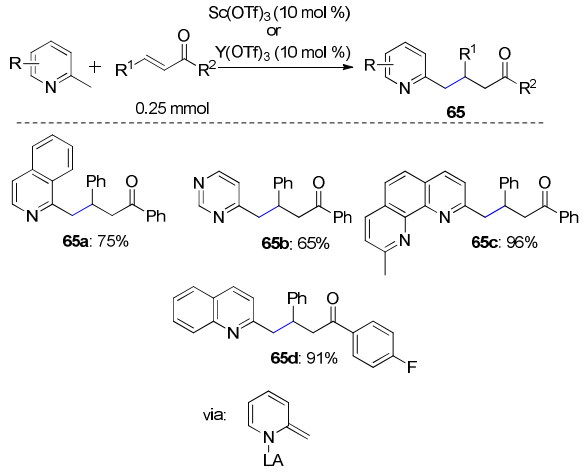
Shaikh *et al.* reported triflic acid promoted C-H bond functionalization of 2-alkyl azaarenes with α-trifluoromethylated imino esters (Scheme 64).[123] Protonation of nitrogen of the azaarene is supposed to trigger the formation of enamine type intermediate, which facilitates nucleophilic addition to provide the product.



Scheme 64 Shaikh's approach for addition of methylazarenes to C=N

3.4.2 Addition to C=C bond.

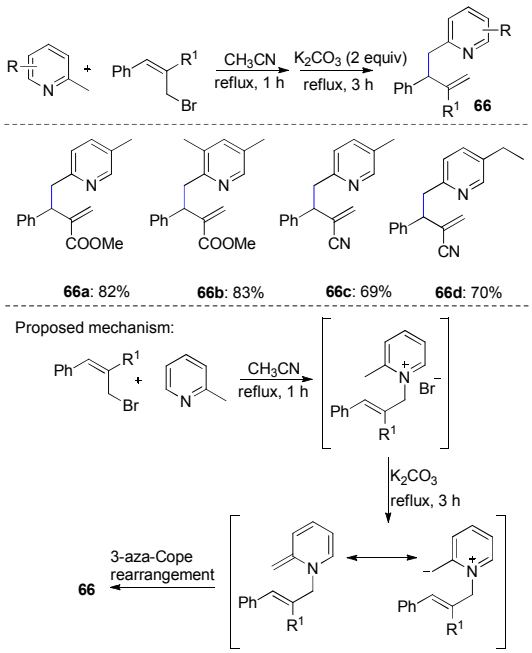
Matsunaga and Kanai showed the $Sc(OTf)_3$/ $Y(OTf)_3$ promoted direct addition of alkyl-substituted azaarenes and benzoxazoles to enones (Scheme 65).[124] Methyl-substituted pyridine, quinoline, isoquinoline, pyrimidine, phenanthroline, and benzoxazole underwent the reaction smoothly. A metal-enamide species has been hypothesised to be an active intermediate. Teo *et al.* later reported a cobalt catalysed version of the reaction with extended substrate scope.[125]



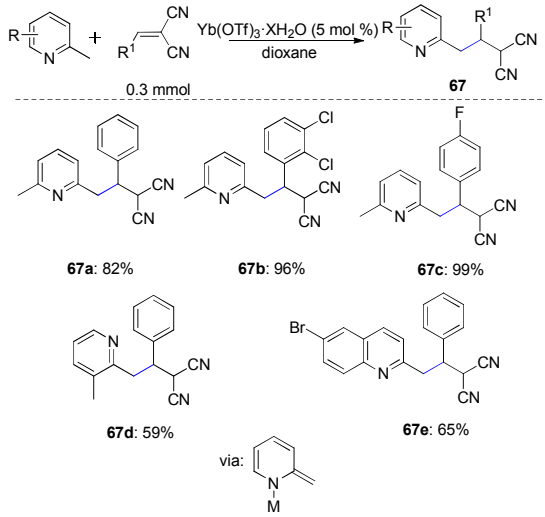
Scheme 65 Matsunaga and Kanai's approach for addition of methylazarenes to enones.

Kim *et al.* have reported a regioselective introduction of 2-methylpyridines to the Baylis–Hillman adducts (Scheme 66).[126] The treatment of 2-methylpyridinium salt of Baylis–Hillman bromide with base is assumed to generate *N*-allylenamine intermediate which undergoes a facile 3-aza-Cope rearrangement under mild conditions to produce the product.

Zhang *et al.* have synthesized different functionalized indolizines via copper-catalyzed annulation of 2-alkylazaarenes with α,β-unsaturated carboxylic acids.[127]



Scheme 66 Kim's approach for addition of methylazarenes to C=C bond of Baylis-Hillman adduct.

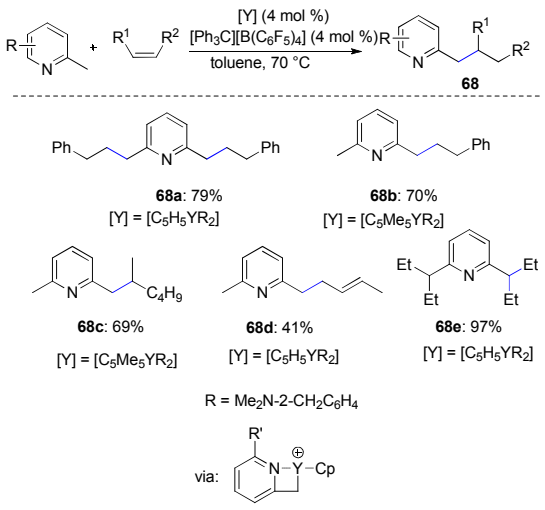


Scheme 67 Huang's approach for addition of methylazarenes to methylenemalononitrile.

Huang *et al.* have reported a Lewis acid catalyzed nucleophilic addition of 2-methylazaarenes to methylenemalononitriles in the presence of $Yb(OTf)_3{\cdot}XH_2O$ in dioxane at 120 °C for 24 h (Scheme 67).[128] Liu and Wang reported a nucleophilic addition of azaarenes to electron-deficient olefins such as *N*-phenylmaleimides without using any catalyst and additive adopting similar strategy.[129] Meshram *et al.* reported a catalyst-free aqueous addition of azaarenes to various β-nitro styrenes under microwave irradiation.[130]

Hou *et al.* have developed a cationic half-sandwich yttrium alkyl complex catalysed addition of various 2,6-dialkyl-

substituted pyridines to a variety of olefins such as ethylene, 1-hexene, styrenes, and 1,3-conjugated dienes to afford a number of new alkylated and allylated pyridine derivatives (Scheme 68).[131]



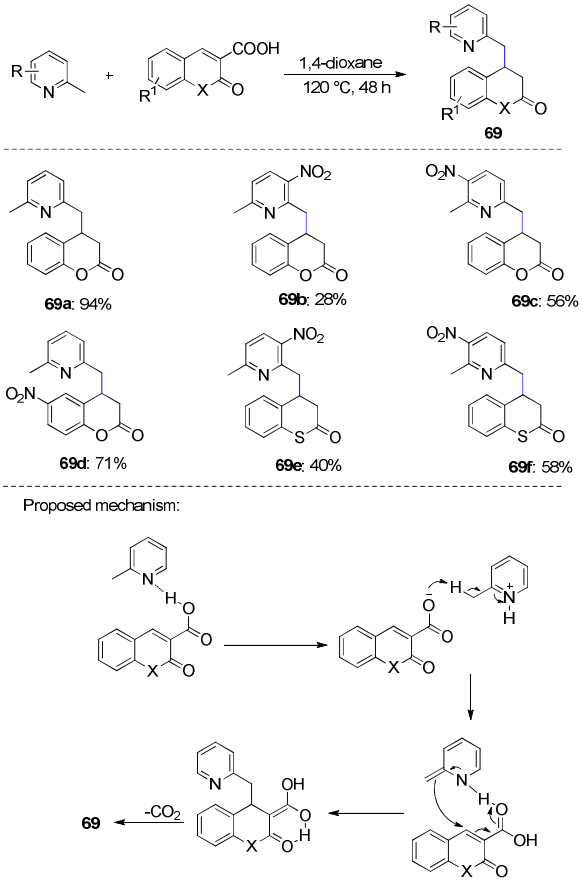
Scheme 68 Hou's approach for addition of azaarenes to olefins.

In 2014, Xiao *et al.* reported the catalyst-free C–H functionalization of 2-alkylazaarenes with (thio)coumarin-3-carboxylic acids via addition and decarboxylation to provide the azaarene-substituted 3,4-dihydro(thio)-coumarins (Scheme 69).[132] Several substituted coumarins and thio-coumarins were employed in the reaction. The same strategy was extended to the reaction of 4-oxo-4H-chromene-3-carboxylic acids with azaarenes to construct azaarene 2-substituted chromanones.[133]

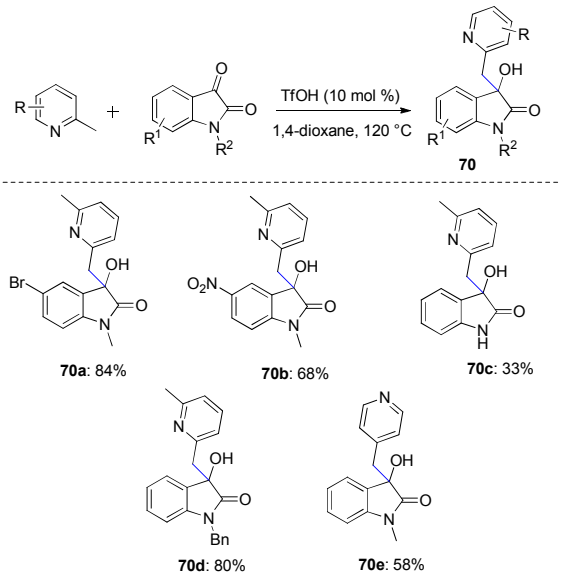
3.4.3 Addition to C=O bond.

Xiao and Li have investigated a Brønsted acid catalyzed functionalization of sp^3 C-H bonds in 2-methylazaarenes with isatins to provide a facile access to biologically important azaarene-substituted 3-hydroxy-2-oxindoles (Scheme 70).[134] The reaction was achieved in the presence of triflic acid catalyst in dioxane at 120 °C. A variety of *N*-substituted isatins containing both the electron-donating and electron–withdrawing substituents including halogens in the isatin phenyl ring were well-tolerated. Meshram *et al*. reported the synthesis of azaarene-substituted 3-hydroxy-2-oxindoles under catalyst-free conditions in water using microwave irradiation,[135] Lee *et al.* reported iodine catalysed version of the reaction,[136] Reddy *et al*. reported PEG-400 as a reaction medium for achieving the reaction.[137] Our group has reported the use of TBAF as catalyst,[138] and Kumar *et al.* have explored β-cyclodextrin catalysed version of the reaction.[139]

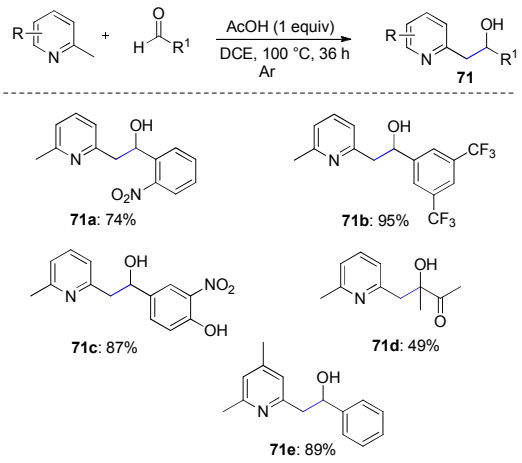
Yang *et al*. have reported an acetic acid promoted nucleophilic addition of 2-methylazaarenes to aldehydes (Scheme 71).[140] Aldehydes with electron-withdrawing substituents afford products in good yields. Substituted azaarenes also participate well in the reaction. Meshram *et al.* have carried out nucleophilic addition of 2-methyl azaarenes to aldehydes in water.[141] Wang *et al.* have investigated an ionic liquid promoted nucleophilic addition of alkyl azaarenes to aldehydes.[142] Wang *et al.* have also studied a series of



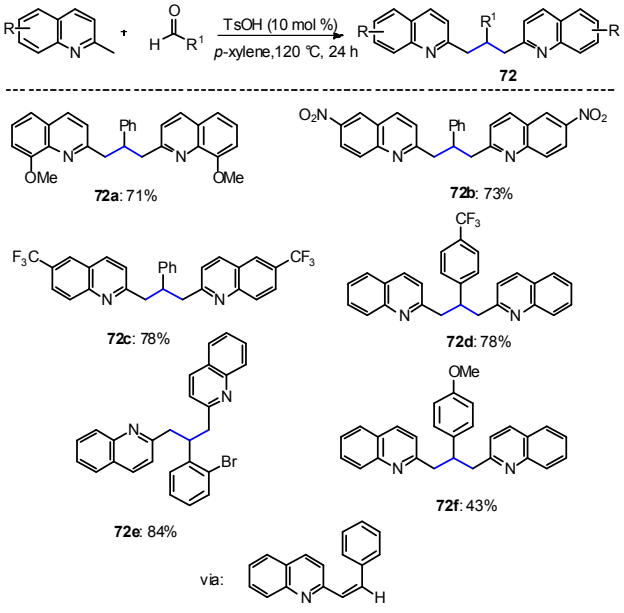
Scheme 69 Xiao's approach for tandem addition and decarboxylation of azaarenes with (thio)coumarin-3-carboxylic acids.



Scheme 70 Xiao and Li's approach for nucleophilic addition of azaarenes to isatins.



Scheme 71 Yang's approach for nucleophilic addition of azaarenes to aldehydes.



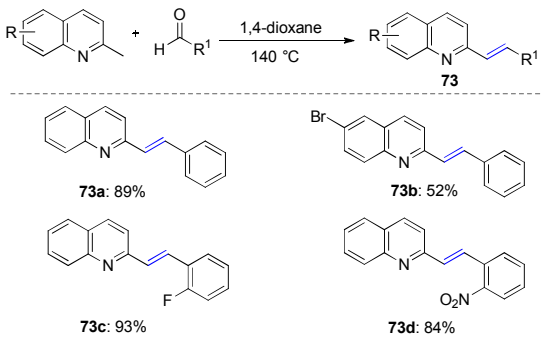
Scheme 72 Niu and Guo's approach for the synthesis of 1,3-di(2-quinolyl)propane derivatives.

-Lewis-acid-catalyzed nucleophilic reactions of 2-methylazaarenes with aldehydes; 2-(pyridin-2-yl)ethanols with common substituents were formed through the $LiNTf_2$ promoted aldol reaction, 2-alkenylpyridines were synthesized exclusively in the (E)-form in the presence of $LiNTf_2$ and H_2NTf, and 2-alkenylquinolines were obtained by the reaction of 2-methylquinolines and aldehydes using $La(Pfb)_3$ as catalyst.[143]

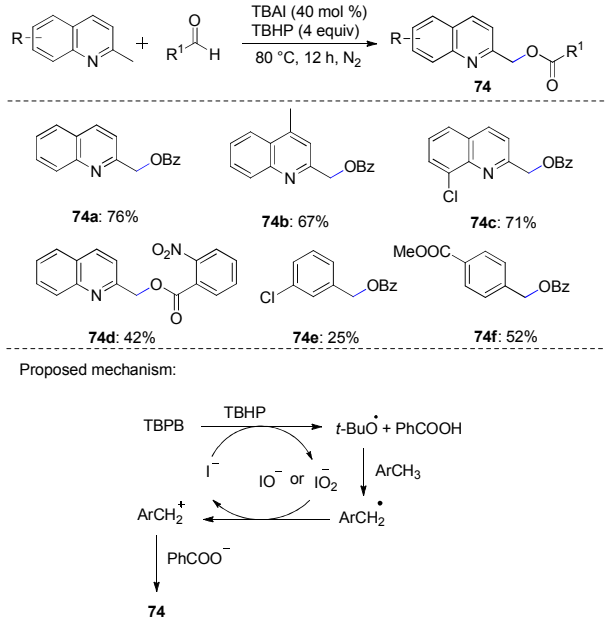
Niu and Guo have reported tosic acid catalyzed reaction of 2-methyl azaarenes and aromatic aldehydes to give 1,3-di(2-quinolyl)propane derivatives (Scheme 72).[144] 2-Alkyl quinolines with electron-neutral, electron-donating or electron-withdrawing groups are examined in the reaction.

Xiao *et al.* reported a facile approach to synthesize (E)-2-alkenylquinoline derivatives of 2-methylquinolines with aldehydes under catalyst-free conditions (Scheme 73).[145] Several substituted aldehydes and 2-alkylquinolines take part in the reaction, tolerating functional groups such as Cl, Br, OMe, and NO_2.

Wang *et al.* have developed an efficient acyloxylation of alkylarenes with aromatic aldehydes using TBAI and TBHP catalytic system (Scheme 74).[146] Functional groups such as fluoro, chloro, bromo, methoxy, nitro, and methyl group are compatible with the reaction conditions. It is postulated that TBPB, formed from benzaldehyde and TBHP, is the reaction intermediate. TBHP and TBPB are decomposed by the iodide ion to generate a *tert*-butoxyl radical and benzoic acid. The iodide ion is oxidized to corresponding (hypo)iodite. Subsequently, the *tert*-butoxyl radical or (hypo)iodite abstracts a hydrogen atom from the benzylic C–H bond of alkylarene to afford benzylic radical, which is re-oxidized quickly by (hypo)iodite to provide benzyl cation. The reaction of benzyl cation with the benzoate anion finally affords the ester.

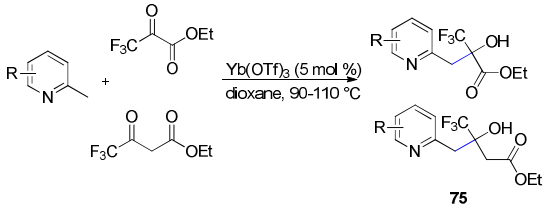


Scheme 73. Xiao's approach for alkenylation of azaarenes with aldehydes.



Scheme 74 Wang's approach for acyloxylation of azaarenes with aldehydes.

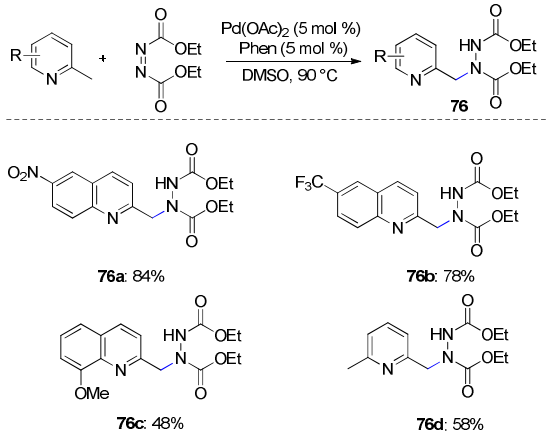
Shaikh *et al.* reported the nucleophilic addition of 2-methylazaarenes to α-trifluoromethylated carbonyl compounds using $Yb(OTf)_3$ as catalyst (Scheme 75).[147] Several substituted azaarenes and carbonyl compounds were employed in the reaction. Zhou and Zou have also studied the reaction in the presence of $Fe(OAc)_2$ with moderate to good yields.[148]



Scheme 75 Shaikh's approach for nucleophilic addition of 2-methylazaarenes to α-trifluoromethylated carbonyls.

3.4.4 Addition to N=N bond.

Qu and Guo have accomplished the amination of 2-alkyl azaarenes with N=N double bond containing azodicarboxylates under $Pd(OAc)_2$ catalysis (Scheme 76).[149] Various 2-alkyl quinolines with electron-neutral/donating/withdrawing groups were tested and worked well. However, the reaction conditions using Pd catalysis were not appropriate to pyridine derivatives, and it required the replacement of $Pd(OAc)_2$ by $Cu(OTf)_2$ (**76d**, 58%). Huang *et al.* later reported $Cu(OTf)_2$ catalysed version of the reaction.[150]

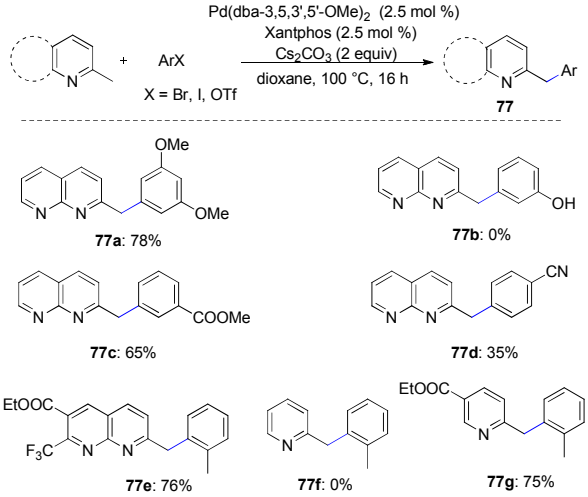


Scheme 76 Qu and Guo's approach for amination of azarenes.

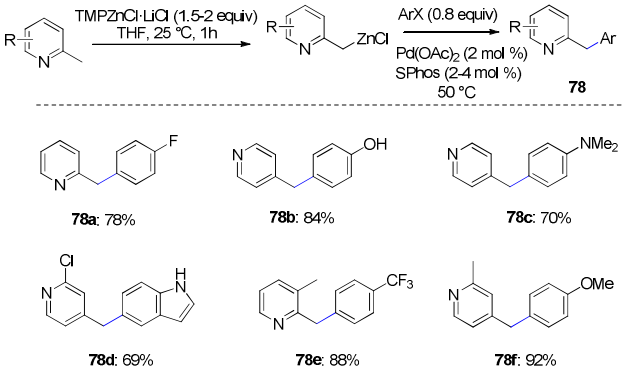
3.4.4 Some other reactions of methylazaarenes.

Morris *et al.* have brought about a selective mono arylation of benzylic C-H bond of methylazaarenes with aryl halides using $Pd(dba\text{-}3,5,3',5'\text{-}OMe)_2$ as catalyst and Xantphos as ligand (Scheme 77).[151] Azaarenes and aryl halides with various structural features participate nicely in the reaction. Li *et al.* reported diarylation of azaarenes with arylhalides using palladium acetate.[152]

Knochel *et al.* have developed a direct Negishi type cross coupling of 2-picoline and 4-picoline derivatives via zincation with TMPZnCl·LiCl, followed by cross-coupling with numerous substituted aryl bromides in the presence of palladium catalyst (Scheme 78).[153]



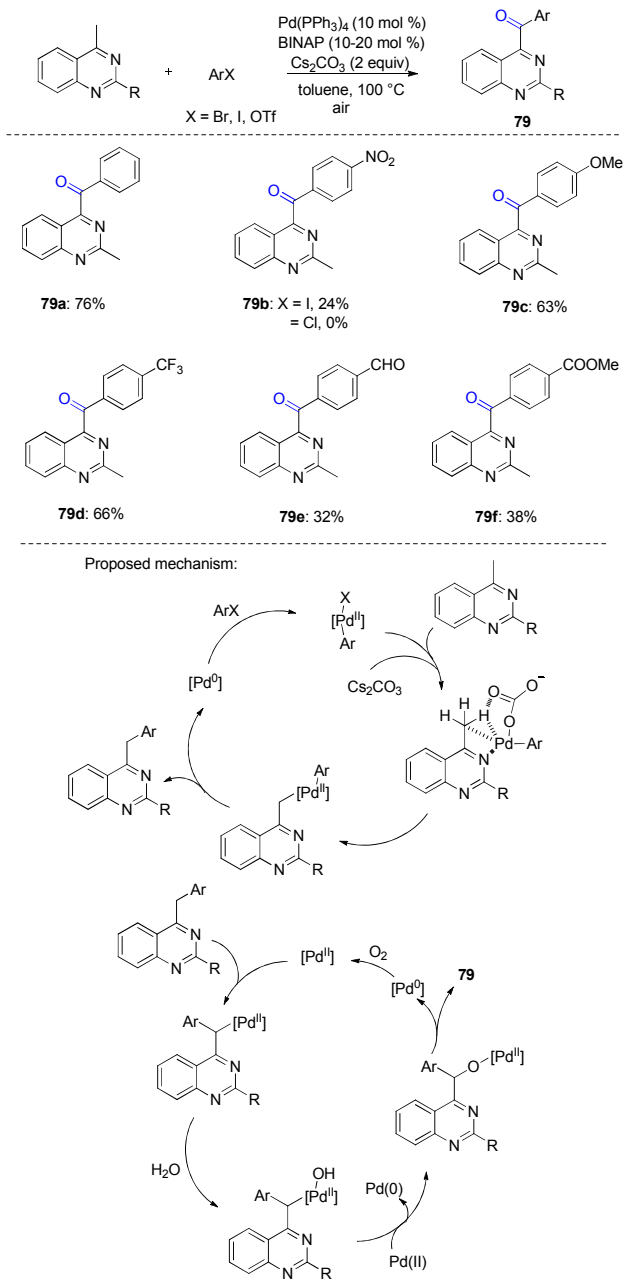
Scheme 77 Morris's benzylic C-H arylation of azaarenes.



Scheme 78 Knochel's benzylic C-H arylation of azaarenes.

Li *et al.* reported Pd(0)-catalyzed C-H bond arylation/oxidation of 4-methylquinazolines by aryl bromides in the presence of $Pd(PPh_3)_4$/BINAP under air (Scheme 79).[154] The mechanism proceeds through an arylated intermediate, which is then oxidised to the corresponding product.

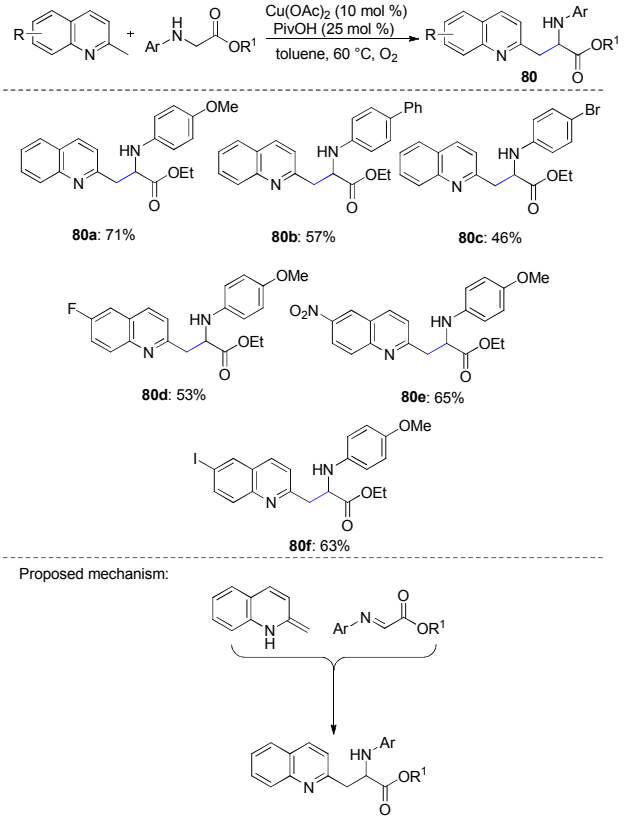
Huang *et al.* have accomplished the synthesis of β-quinolinyl α-amino acid esters via cross dehydrogenative coupling reaction of methylquinoline derivatives and *N*-aryl glycine esters by cooperative catalysis of copper salt and Brønsted acid (Scheme 80).[155] Several substituted quinoline derivatives and aryl glycine ester detivatives work well in the reaction with excellent functional group tolerance. According to the probable mechanism given by the authors, 2-methylquinoline is initially tautomerized into the enamine intermediate under the catalysis of PivOH as a Brønsted acid. The more reactive enamine then nucleophilically attacks the imine, resulting from the oxidation of glycine ester, to give the desired product.



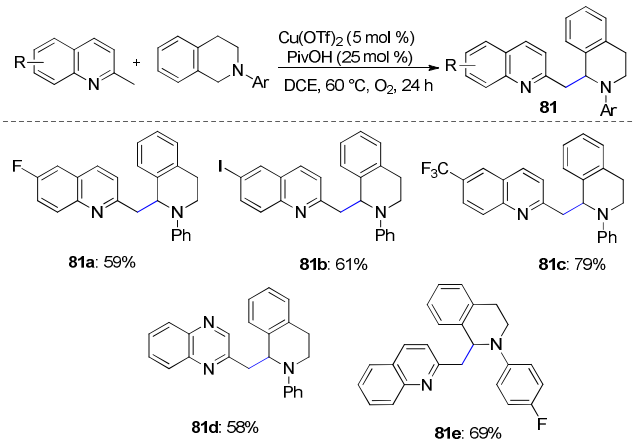
Scheme 79 Li's benzylic C-H arylation/oxidation of azaarenes.

Yang *et al.* have carried out copper/Brønsted acid catalysed cross dehydrogenative coupling of methylquinoline derivatives with tetrahydroisoquinolines in the presence of $Cu(OTf)_2$ and PivOH as co-catalyst under mild reaction conditions (Scheme 81).[156] Reaction shows wide substrate scope with good functional group tolerance.

Zhou and Yin have reported the synthesis of 2-hetarylquinazolin-4(3H)-ones from 2-aminobenzamides and 2-methylazaarenes via copper catalysed oxidative amination and cyclisation (Scheme 82).[157] The reaction was best achieved in the presence of CuCl and Ph_2PO_2H. The proposed mechanism passes through the intermediate **i16**, which undergoes cyclisation to give the product.



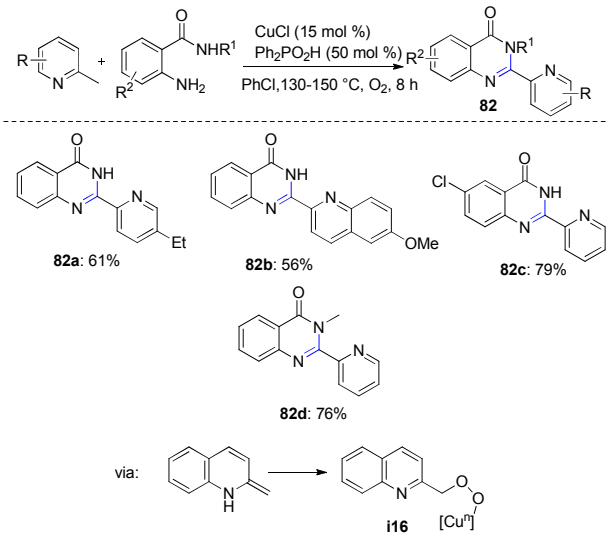
Scheme 80 Huang's approach for the synthesis of β-quinolinyl α-amino acid esters via CDC.



Scheme 81 Yang's approach for coupling of methylquinoline derivatives with tetrahydroisoquinolines via CDC.

Xiao and Deng have reported the synthesis of 2-sulfolmethyl quinoline derivatives from 2-methylquinoline and sodium sulfinates in the presence of KI and TBHP (Scheme 83).[158] Various sodium sulfinates and 2-methylquinolines were explored in the reaction. Substituents and functional groups

such as halogens, hydroxyl, trifluoromethyl, and trifluoromethoxy survived well in the reaction. Addition of radical scavenger inhibits the reaction thereby indicating a radical pathway. Oxygen centered radical, generated by oxidation of sulfinate with an iodide radical, can be resonated to a sulphonyl radical. Addition of the sulphonyl radical to enamine intermediate, formed from 2-methylquinoline by the Brønsted acid-promoted isomerization, affords another intermediate, which can be further oxidized by an iodide radical to provide the product.



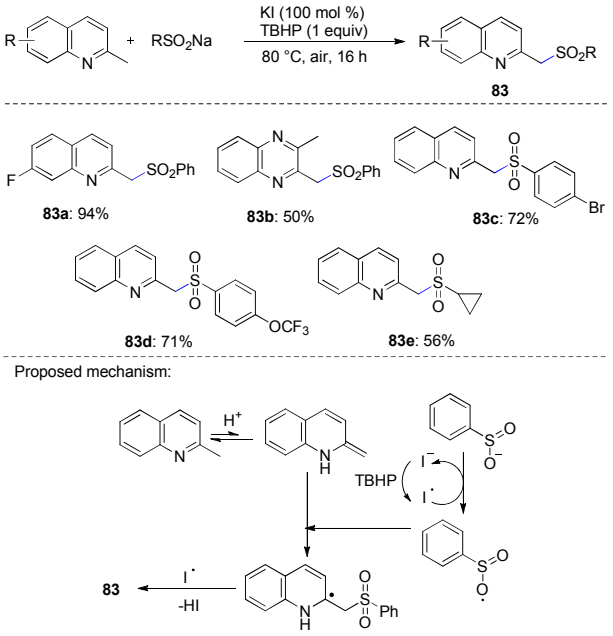
Scheme 82 Zhou and Yin's approach for the synthesis of 2-hetarylquinazolin-4(3H)-ones.

Yang *et al.* have shown an interesting Brønsted acid promoted nucleophilic addition of 2-methylazaarenes to nitroso compounds affording azaarene-2-aldimines, azaarene-2-carbaldehyde, or azaarene-2-oximes selectively (Scheme 84).[159] *p*-Nitrobenzoic acid (50 mol%) was found to be optimal for nucleophilic addition of azaarene to nitroso compound. Several substituted 2-methylquinolines and nitroso compounds react nicely and show good functional group tolerance. When the reaction is carried out with *t*-butyl nitrite, the nucleophilic addition product is the oxime.

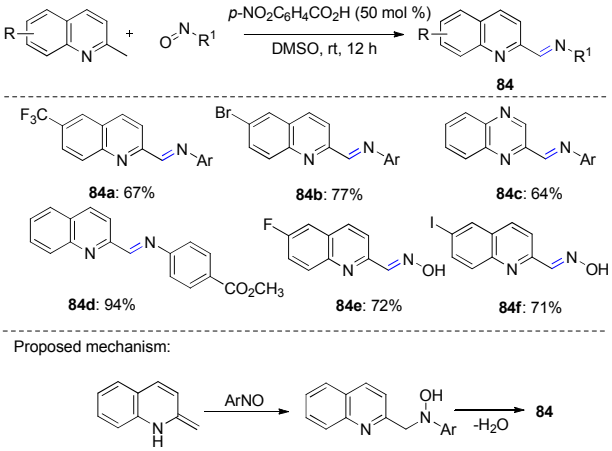
Nguyen *et al.* have interestingly utilized picoline derivatives for the synthesis of 2-heteroaryl-benzimidazoles and benzoxazoles from 2-amino/hydroxy nitrobenzenes using iron and sulphur catalytic system (Scheme 85).[160] 2- or 4-Methyl substitutions were identified as prerequisites of the reaction.

Nguyen *et al.* have also reported the synthesis of 2-heteroarylbenzothiazoles from 2-halonitroarenes and methylarenes using elemental sulphur (Scheme 86).[161] A probable mechanism is also outlined in the Scheme.

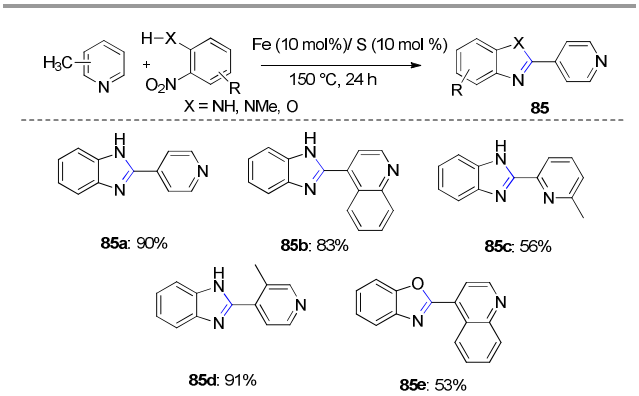
There are some other valuable contributions made in this direction such as, Mashima *et al.* reported coupling of alkynes and 2-alkylpyridines,[162] Liu *et al.* performed nitration,[163] Tian *et al.* carried out olefination of secondary amines with azaarenes using DDQ,[164] Pan and Chen accomplished the synthesis of indolizines from propargyl alcohols and



Scheme 83 Xiao and Deng's approach for the synthesis of 2-sulfolmethyl quinoline.

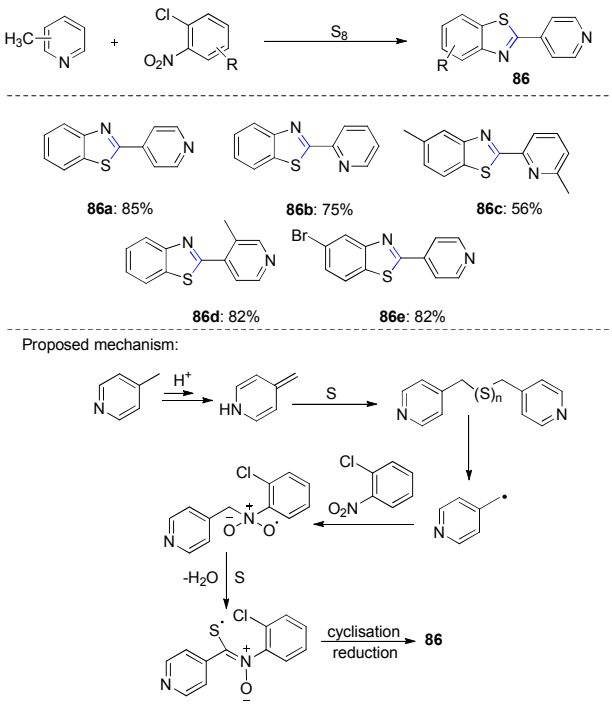


Scheme 84 Yang's approach for nucleophilic addition of 2-methylazaarenes to nitroso compounds.



Scheme 85 Nguyen's approach for the synthesis of 2-hetarylbenzimidazoles and –benzoxazoles from azaarenes.

azaarenes,[165] and Kumar *et al*. realized the synthesis of alkyl azaarens pyridinium zwitter ions.[166]



Scheme 86 Nguyen's approach for the synthesis of 2-hetarylbenzothiazoles from azaarenes.

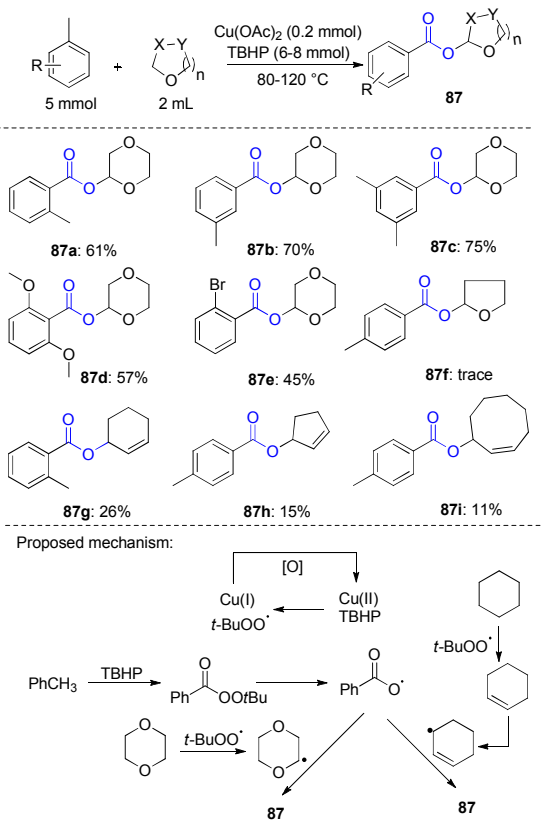
4. Methylarenes as carboxylate source.

Rare examples of such type of reaction are reported by Patel *et al*. using Cu(II) and TBHP combination. The reaction of methylarenes with cyclic ethers results in the formation of α-acyloxy ethers, whereas that with cycloalkanes gives rise to allyl esters (Scheme 87).[167] According to the mechanism proposed by authors, methylarenes are initially converted to benzaldehydes by the action of copper and TBHP. The *tert*-butylperoxy radical, generated from TBHP, adds to benzaldehyde providing *t*-butyl benzoperoxate. Homolytic cleavage of peroxy species affords benzoxy radical along with *t*-butoxyl radical. Equally, abstraction of α-ethereal hydrogen from dioxane gives rise to another radical intermediate, which on coupling with benzoxy radical leads to the formation of the product.

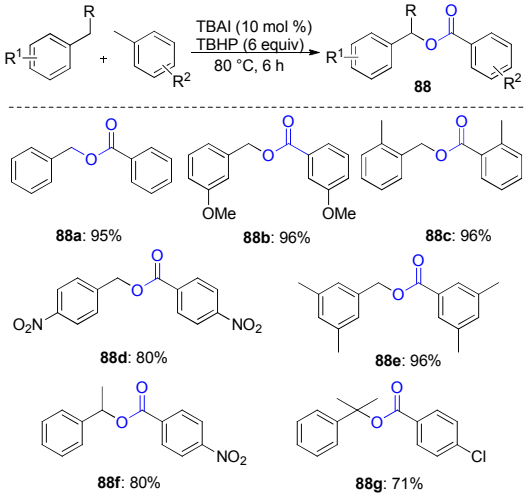
Patel *et al.* have also achieved the synthesis of both the symmetrical as well as unsymmetrical benzylic esters via a novel strategy using alkylbenzene in the presence of TBAI/TBHP (Scheme 88).[168] Alkylbenzene as a self- or as a cross-coupling partner via the intermediacy of Ar–COOH, and the benzylic carbocation obtained from the other half of the alkylbenzene, are responsible for the reaction.

5. Methylarenes as an alcohol source.

Patel *et al.* have successfully employed methylarenes as an alcohol source (Scheme 89).[169] The reaction of methylarenes with aldehydes in the presence of $Cu(OAc)_2$ and TBHP gives rise to the formation of esters in moderate to good yields. Several substituted methylarenes and aldehydes were used in the reaction. Formation of benzyl alcohol in the reaction mixture was observed. The proposed mechanism by the

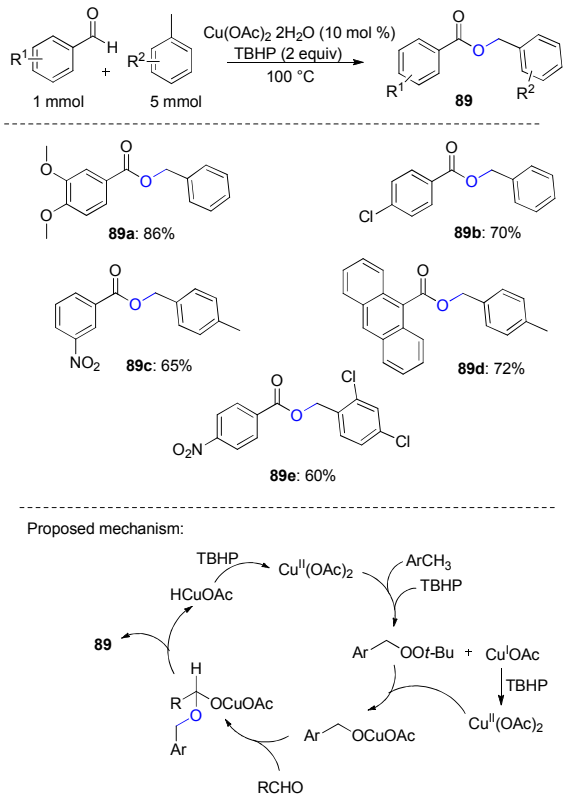


Scheme 87 Patel's approach for esterification of alkylarenes with methylarenes.



Scheme 88 Patel's approach for homo coupling of methylarenes.

authors involves the coupling of aldehyde and the *in situ* generated alcohol via a hemiacetal intermediate.



Scheme 89 Patel's approach for esterification of aldehydes with methylarenes.

Conclusions

Over the past 10 years, significant progress has been made in the selective utilisation of methylarenes for the synthesis of various values added chemicals. Especially the last 5-6 years have witnessed a drastic development in this area. Advent of selective functionalization of C-H bonds has influenced this area to such an extent that the methylarenes are now unambiguously considered to be "reactive". As a result, methylarenes have grasped the foremost advancement for selective formation of C-C and C-X bonds. The contents of the review have been classified into the categories depending upon the nature of the involvement of methylarenes, and only latest and important findings have been dealt with. Yet, many of the reactions described severely suffer from the drawbacks such as excessive use of methylarenes and oxidants, and poor yields. To further progress this area, the formidable challenge to synthetic chemists is to develop sustainable technologies in a more economic and environmentally benign way for efficient coupling of methylarenes under mild reaction conditions, and to unravel the underlying mechanisms. The area has immense future but should not be confined to simple extrapolation of the past developments. Some spectacular developments are likely in this exciting and rewarding area of research.

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