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Palladium-Catalyzed *meta*- and *para*-C–H Bond Functionalizations Assisted by a Directing Group

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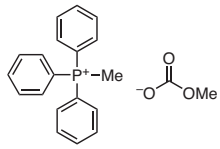
Cattelan, L.; Noè, M.; Selva, M.; Demitri, N.; Perosa, A. *ChemSusChem* **2015**, *8*, 3963.



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City Hall at Thorn (oil on canvas, 50.7 × 80 cm) was painted in 1848 by Johann Philipp Eduard Gaertner (1801–1877), a prominent 19th-century vedutista of mostly Berliner cityscapes. He was born, raised, and spent most of his life in Berlin. His art training consisted of an apprenticeship, in his teens, at the Royal Porcelain Factory and lessons at the Academy of Arts (Berlin). This was supplemented by a two-year stint with the landscapist Jean-Victor Bertin in Paris. His work-related travels took him to Russia, Austria, Bohemia, and many parts of Prussia. As happens with many presently famous artists, his reputation and output waned in his later years and his oeuvre was almost forgotten until the latter part of the twentieth century.

Detail from ***City Hall at Thorn***. Photo courtesy National Gallery of Art, Washington, DC.

Most of his early paintings, and the ones he is best known for, were commissioned by royal patrons in Prussia and Russia. His many cityscapes of Berlin chronicled the rapidly changing urban landscape of the city. Gaertner's meticulously executed urban scenes, as in the present painting,* underscore his exacting style and attention to detail, including the effects of light and shadow, and is suggestive of his possible use of a camera obscura to create his sketches.

This painting is a gift of Ethel Gaertner Pyne to the National Gallery of Art, Washington, DC.

* *Gaertner's cityscapes are often so accurate, they are almost photographic. To find out more, visit* ***SigmaAldrich.com/acta503***

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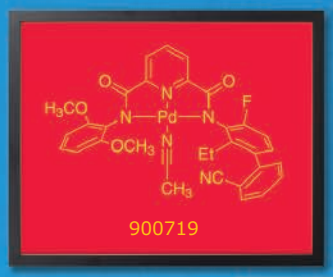

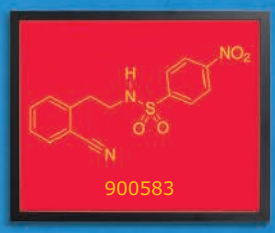

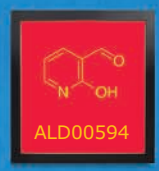

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Palladium-Catalyzed *meta*- and *para*-C–H Bond Functionalizations Assisted by a Directing Group


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Keywords. remote C–H functionalization; *meta*-selectivity; *para*-selectivity; chelation-assisted; palladium catalysis.

Abstract. Direct and site-selective functionalization of unactivated C–H bonds is becoming a powerful strategy of organic synthesis in academia and industry. While *ortho*-selective C–H functionalizations are well-established, chelation-assisted remote *meta*- and *para*-C–H bond functionalizations remain a noteworthy challenge. This article reviews significant and very recent advances in the palladium-catalyzed, directed *meta*- and *para*-C–H functionalizations of aromatic compounds, and covers the literature from 2015 to mid-2017.

Outline

1. Introduction

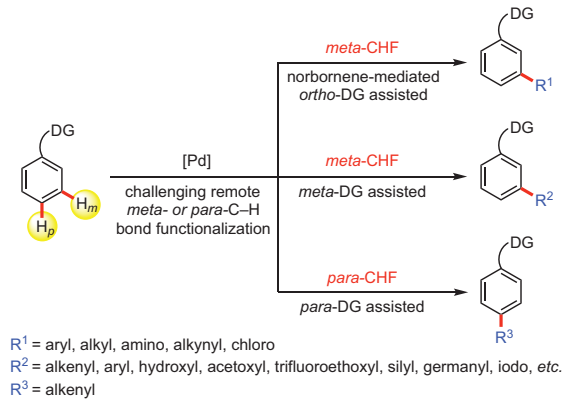
The site-selective functionalization of aromatic compounds has significant applications in natural product synthesis and in the chemistry of materials, pharmaceuticals, and polymers.[1–3] In this regard, the efficient *ortho*-, *meta*-, or *para*-selective C–H functionalization (CHF) of aromatic compounds is of paramount importance and an outstanding challenge.[4–6] The last decades have witnessed the rapid and extensive development of the transition-metal-catalyzed, *ortho*-selective CHF of arenes with the assistance of various directing groups (DGs).[7–10] In contrast, only a small number of reports exist on the *meta*-selective CHF of arenes.[11–14] One major reason for this dearth of reports is that common DGs are generally unable to assist the metal in reaching the ring meta position due to the strain of the corresponding metallacycle intermediate. Moreover, while several protocols of the *para*-selective CHF of arenes have been disclosed, they still suffer from limitations in substrate scope and poor selectivity. Since these protocols often rely on electronic and steric factors to direct the selectivity, the *para*-selective activation of common arenes remains extremely challenging.[15]

Palladium salts are playing an increasingly important role in *meta*- and *para*-C–H activation strategies that are based on directing groups,[13–15] and these strategies include three major types (**Scheme 1**). The first is the very recently developed norbornene-mediated, *meta*-C–H functionalizations assisted by an *ortho*-directing group. The second is *meta*-CHFs of arenes assisted by *meta*-directing groups. The third type uses a novel template-based approach for *para*-CHFs. Because a number of recent reviews have dealt with this general topic,[6,12–15] we will limit our discussion to the literature covering palladium-catalyzed, directing-group-assisted *meta*- and *para*-CHFs of aromatic compounds from 2015 to mid-2017.

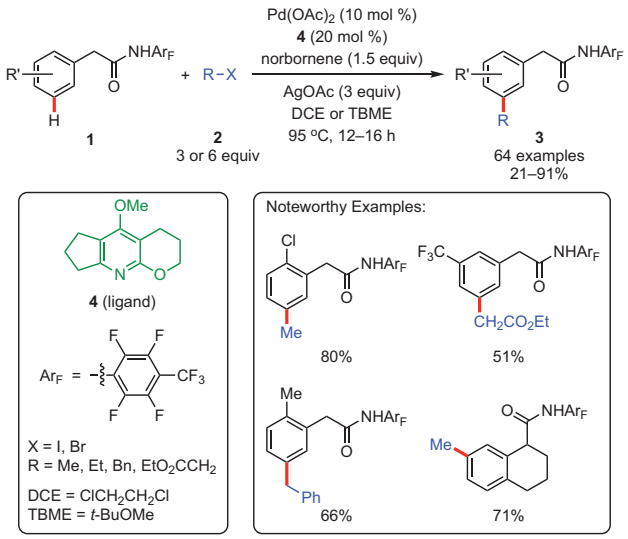
2. Norbornene-Mediated *meta*-C–H Functionalization Assisted by *ortho*-Directing Groups (DGs)

2.1. Arylation and Alkylation

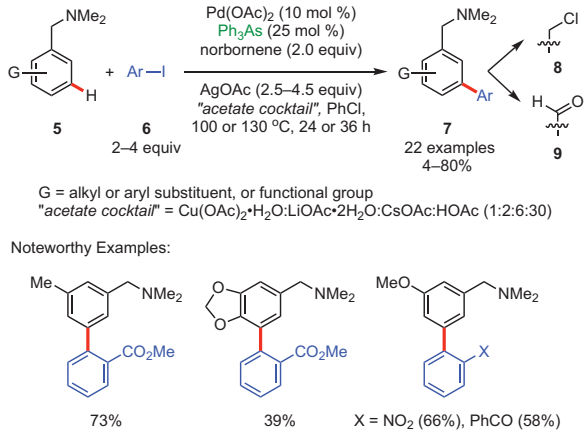
The unique reactivity of norbornene in palladium-catalyzed functionalization reactions was disclosed in 1997 by Catellani and co-workers in the regioselective synthesis of *o*,*o*'-disubstituted vinylarenes from aryl iodides.[16,17] This unique reactivity is the result of the differences in the reactivity of the palladium(0), palladium(II),



Scheme 1. Three Major Types of Directing-Group-Assisted *meta*- or *para*-C–H Bond Functionalization.



eq 1 *(Ref. 18)*



Scheme 2. Norbornene-Mediated *meta*-C–H Arylation of Benzylamines. *(Ref. 19)*

and palladium(IV) species formed in the catalytic sequence with norbornene acting as a transient mediator.

Inspired by Catellani's reports, Yu and co-workers developed the first norbornene-mediated catalytic *meta*-C–H activation using simple and common *ortho*-directing groups.[18] Catalyzed by palladium acetate, mediated by norbornene, and promoted with electron-rich pyridine- or quinoline-based ligands, phenylacetic acid derivatives **1** were selectively alkylated or arylated at the *meta*-position with electrophiles **2** including methyl iodide, ethyl iodoacetate, and various organohalides (**eq 1**).[18]

In the proposed catalytic cycle of this transformation, initial *ortho*-C–H activation leads to an *ortho*-palladacycle, which undergoes a norbornene-mediated, Catellani-type carbopalladation to form a five-membered palladacycle. Reaction of this palladacycle with the coupling partners, **2**, forms the new *meta*-C–C bond. Subsequent β-elimination of norbornene followed by proto-demetallation forms the desired products, **3**, and regenerates the palladium catalyst.

Simultaneously, Dong and co-workers reported a norbornene-mediated palladium(II)-catalyzed *meta*-C–H arylation of tertiary amines **5** with commercially available Ph_3As as the ligand (**Scheme 2**).[19] Interestingly, the "acetate cocktail" additive—consisting of $LiOAc{\cdot}2H_2O$, CsOAc, and $Cu(OAc)_2{\cdot}H_2O$ (2:6:1) in acetic acid—led to improvements in the reaction rate and yield. Under the optimized reaction conditions, a range of benzylamines, **5**, reacted regioselectively with *ortho*-substituted aryl iodides, **6**, to form *meta*-aryl-substituted products **7**. Products **7** could be easily converted by established procedures into the corresponding benzyl chlorides or aldehydes, which are synthetic precursors of a number of valuable targets.

Some of the limitations of the norbornene-mediated *meta*-CHFs—ineffective coupling with alkyl iodides containing a β-hydrogen and compatibility only with aryl iodides possessing *ortho*-coordinating groups—prompted Yu and co-workers to develop 2-carbomethoxynorbornene (NBE-CO_2Me, **10**) as a more effective transient mediator in the presence of a quinoline-based ligand, **11** (**eq 2**).[20] These conditions suppress the reductive elimination side reaction and promote unprecedented *meta*-alkylation of phenyl acetamides with a wide range of alkyl iodides, as well as *meta*-arylation with aryl iodides lacking ortho substituents.

In 2016, Zhao, Shi, and co-workers reported an approach for achieving the palladium–norbornene catalyzed, selective *meta*-C–H arylation of β-arylethylamine derivatives by taking advantage of an oxalyl amide directing group (**eq 3**).[21] This *meta*-arylation not only tolerates a wide range of electron-donating and electron-withdrawing substituents, but also proceeds well with thiophene derivatives. Notably, this was the first report of a norbornene-mediated, palladium(II)-catalyzed *meta*-CHF assisted by an N,O-bidentate directing group.

Yu's group has demonstrated the versatility of 3-acetamido-2-hydroxypyridine and 3-acetamido-5-trifluoromethyl-2-hydroxypyridine as ligands in promoting the *meta*-C–H arylation of protected anilines, heterocyclic aromatic amines, phenols, and 2-benzyl heterocycles using norbornene as a transient mediator.[22] These ligand scaffolds enable the reaction of a wide range of substrates and coupling partners. These two ligands permitted, for the first time, the *meta*-C–H arylation with heterocyclic aryl iodides as coupling partners, a transformation that can potentially be utilized in drug discovery research. The same research group also reported the first example of a silver-free, gram-scale protocol for this catalytic reaction (**eq 4**).[22]

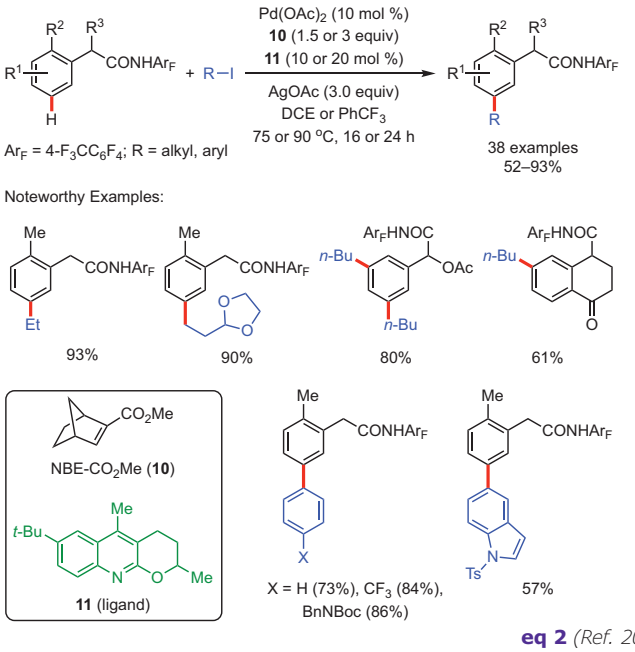
An effective, Pd(II)-catalyzed *meta*-C–H arylation of nosyl-protected phenethylamines, benzylamines, and 2-arylanilines has very recently been disclosed (**eq 5**).[23] This practical and attractive protocol

utilizes 4-acylpyridine as a preferred ligand, a common protecting group (4-nitrophenylsulfonyl or Ns) as directing group, and, for the first time, a catalytic amount of 2-norbornene in most cases. The reaction is compatible with a diverse range of aryl iodides, including heteroaryl iodides, and tolerates aryl bromides bearing *ortho*-coordinating groups.

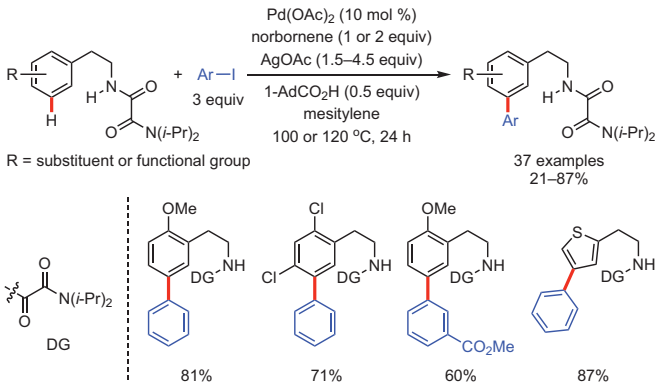
Ling et al. disclosed very recently the first interannular palladium-catalyzed *meta*-selective C–H arylation of biaryl compounds using a 2-trifluoroacetamide as the directing group (**eq 6**).[24] Remarkably, the active catalyst was isolated and shown by X-ray diffraction to be a dimeric palladacycle intermediate consisting of two cyclopalladated trifluoroacetamino biaryl units linked through the trifluoroacetamide. It is worth noting that the interannular *meta*-arylated product from this reaction can be elaborated further, affording various biaryl-2-amine derivatives through *ipso*-alkynylation or directed interannular *ortho*-C–H functionalization of the proximal C–H bond.

The *meta*-C–H arylation of phenylacetic acids could also be achieved, since the weak coordination of the carboxylic acid group results in the Catellani reaction of aryl iodides outcompeting the *ortho*-C–H palladation of phenylacetic acid (**eq 7**, Part (a)).[25] Under the optimized conditions, the reaction was compatible with both electron-rich and electron-deficient substrates as coupling partners and was amenable to scaling up. A similar Pd(II)-**10** catalysis was successfully applied to the *meta*-C–H arylation and alkylation of benzylsulfonamides using isoquinoline as ligand (eq 7, Part (b)).[26] This transformation had a broad substrate scope and excellent functional-group tolerance. Its good compatibility with both heteroaryl iodides and alkyl iodides gives it an advantage over other *meta*-C–H functionalization protocols, and the sulfonamide functional group's broad applications render it highly useful in the synthesis of *meta*-substituted sulfonamides and sulfonate esters, as well as styrene derivatives.

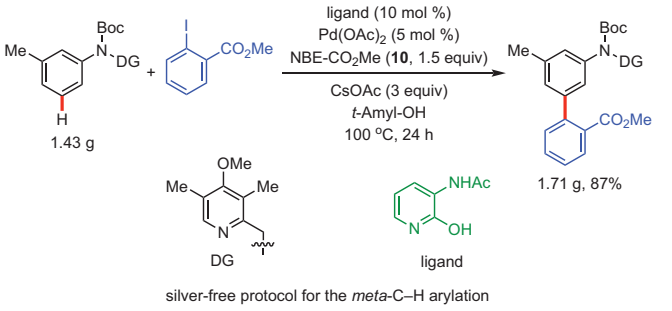
Benzylamines are distinctive structural motifs in many natural products and pharmaceuticals, and a practical and general *meta*-CHF of benzylamines would be helpful in their further elaboration. However,



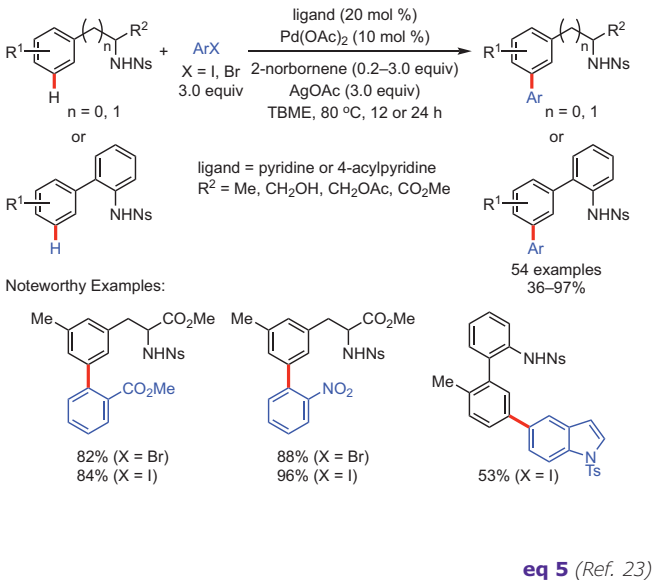
eq 2 *(Ref. 20)*



eq 3 *(Ref. 21)*



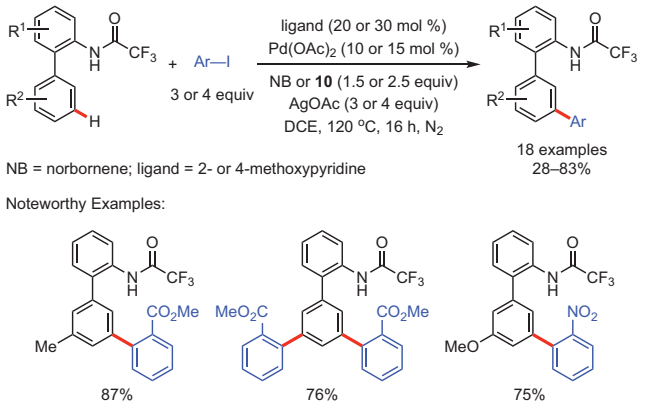
eq 4 *(Ref. 22)*



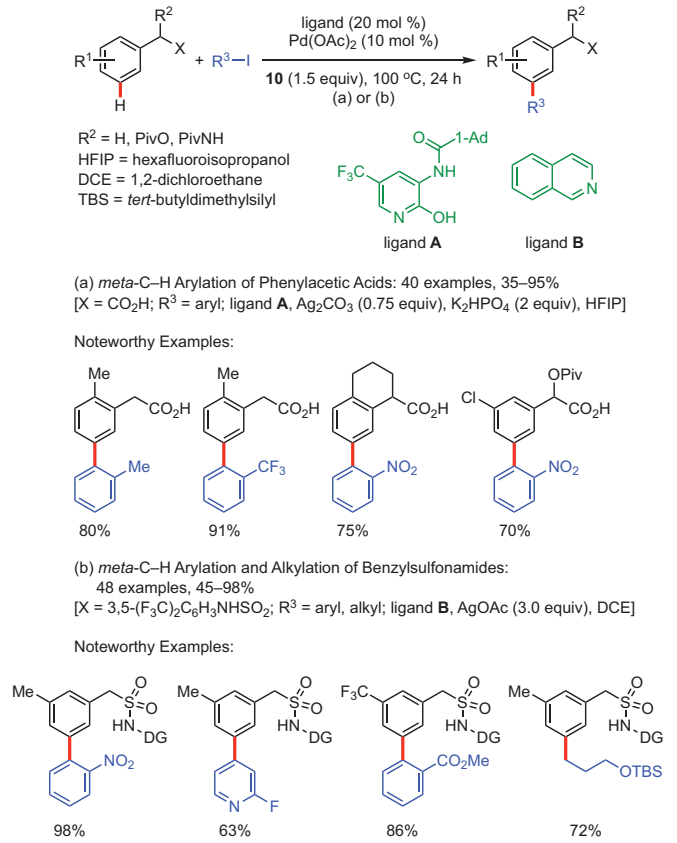
eq 5 *(Ref. 23)*

the reported norbornene-mediated *meta*-CHF of benzylamines has been limited to those aryl iodide coupling partners containing *ortho*-coordinating groups. Yu and co-workers overcame this limitation by using 2-hydroxy-3-trifluoromethylpyridine as ligand and NBE-CO_2Me (**10**) as the transient mediator.[27] The reaction, which is scalable and compatible with a variety of heterocycle-containing substrates and coupling partners, has been used to form a key intermediate in the synthesis of an analogue of the inhibitor RPR128515 (**Scheme 3**).[27]

Very Recently, Li and Ferreira disclosed a *meta*-C–H arylation of benzylic alcohols with an *ortho*-selective, quinoline-based acetal directing scaffold by using the NBE-CO_2Me mediated process.[28] The reaction provided the desired biaryl products in moderate-to-high yields, and exhibited a considerable scope and functional group compatibility. The use of an amino acid based ligand (TFA-Gly-OH) for the transformation is distinct from similar functionalization reactions in which an N-heterocycle is employed as the ligand. Moreover, the cleavage and recovery of the scaffold could be realized in good yields under mild reaction conditions.



eq 6 *(Ref. 24)*



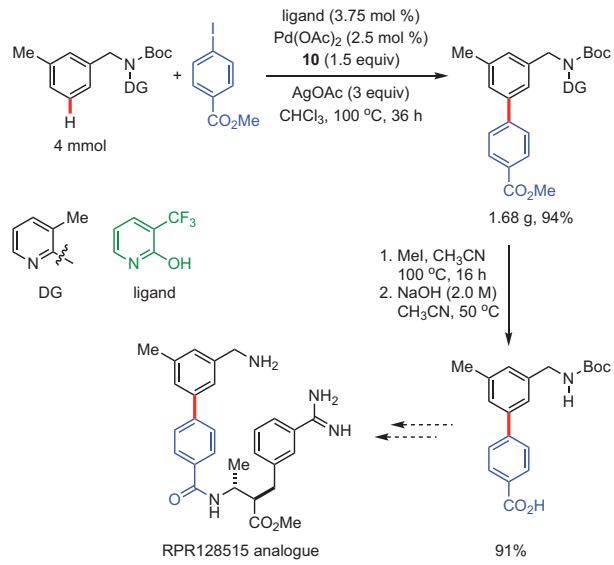
eq 7 *(Ref. 25,26)*

2.2. Amination

The aforementioned norbornene-mediated *meta*-CHFs were limited to alkylations or arylations using alkyl or aryl iodides. In 2016, Yu and co-workers expanded the scope of the reaction to include the *meta*-C–H amination of anilines and phenols with *N*-benzoyloxyamines as the aminating reagents.[29] Both ligand **A** (see eq 7, Part (a)) and NBE-CO_2Me (**10**) were crucial to the success of this transformation. Under the optimal reaction conditions, a variety of substrates were compatible with the reaction, including coupling partners containing other heteroatoms. Moreover, the Boc-protecting group and the pyridine directing group in the products can be removed simultaneously to provide the corresponding free aniline, as in the case of **12**, which is a key intermediate in the synthesis of a BRAF inhibitor (**Scheme 4**).[29]

2.3. Alkynylation

In recent decades, the Sonogashira coupling reaction has become one of the most significant methods for synthesizing arylalkynes, which are important structural motifs in many pharmaceuticals and natural products. However, up until 2016, there had been no reports of alkynylations employing Catellani's norbornene-mediated relay process, when Wang et al. disclosed an NBE-CO_2Me mediated *meta*-C–H alkynylation of anilines (**eq 8**).[29] This *meta*-C–H alkynylation is noteworthy for being compatible with indoline and indazole-containing amines; however, only alkynyl bromides protected with bulky silyl groups afforded *meta*-alkynylated products in acceptable yields.



Scheme 3. Application of the *meta*-C–H Arylation of Benzylamines to the Synthesis of RPR128515 Analogues. *(Ref. 27)*

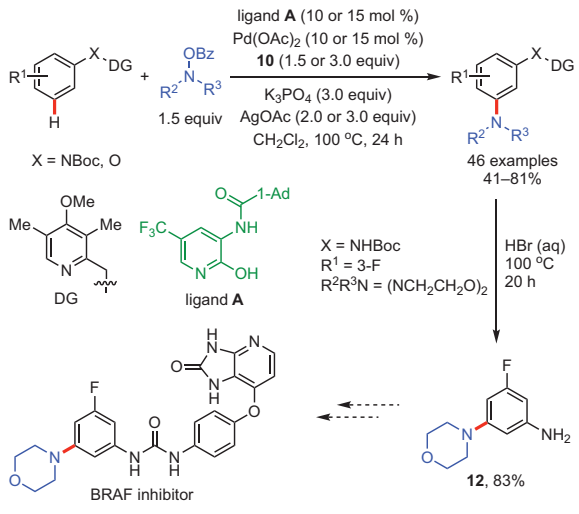
2.4. Chlorination

Given that the versatile reactivity of aromatic halides enables the installation of diverse structural motifs to meet the demands of synthetic applications, the development of the C–H halogenation of arenes would be not only useful but also essential. Shi et al. reported the first example of NBE-CO_2Me mediated *meta*-C–H chlorination of anilines using 2,6-diisopropylphenylchlorosulfate as the chlorinating reagent (**eq 9**).[30] This *meta*-chlorination reaction is promoted by new pyridone-based ligands, displays outstanding functional group tolerance, and leads to high yields of the chlorinated products. Moreover, this *meta*-C–H chlorination was successfully extended to phenols[30] and benzylamines[27] by employing slightly modified conditions.

3. *meta*-C–H Functionalization Assisted by *meta*-Directing Groups

3.1. Nitrile-Based, DG-Assisted *meta*-C–H Functionalization

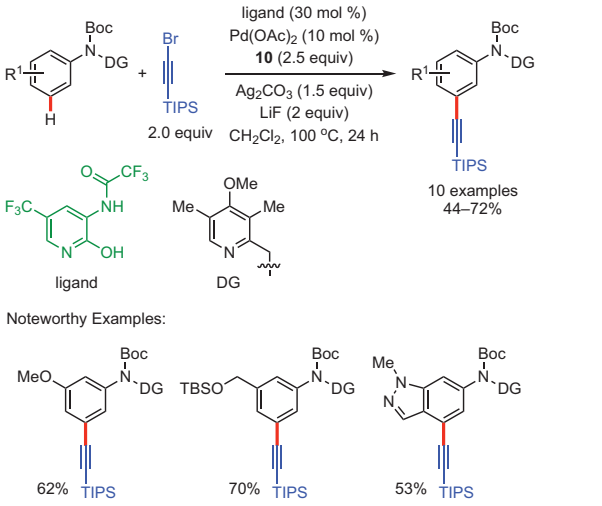
In directed C–H activations, chelation-assisted transformations have been powerful in performing a variety of selective *ortho*-C–H functionalizations.[7–10] However, extending the methodology to perform *meta*-C–H functionalizations has been difficult, since the formation of a cyclophane-like, pre-transition state is energetically and conformationally demanding. In 2012, a significant breakthrough in this respect was achieved by Yu and co-workers, who employed two types of U-shaped, nitrile-based directing groups that resulted in the remote *meta*-C–H olefination of toluene derivatives, hydrocinnamic acids, and 2-biphenylcarboxylic acids.[31] The rational design of the template was predicated on the weak coordination between Pd(II) and the nitrile group in an "end-on" fashion, which was believed to withstand the strain involved in the formation of the cyclophane-like pre-transition state in the *meta*-C–H activation event. This was the first report of a *meta*-C–H activation, via a 12-membered metallacyclic pre-transition state, that is assisted by a cleavable, nitrile-containing *meta*-directing group. It inspired the discovery of diverse *meta*-C–H functionalizations of (hetero)arenes by similar approaches that are discussed below.



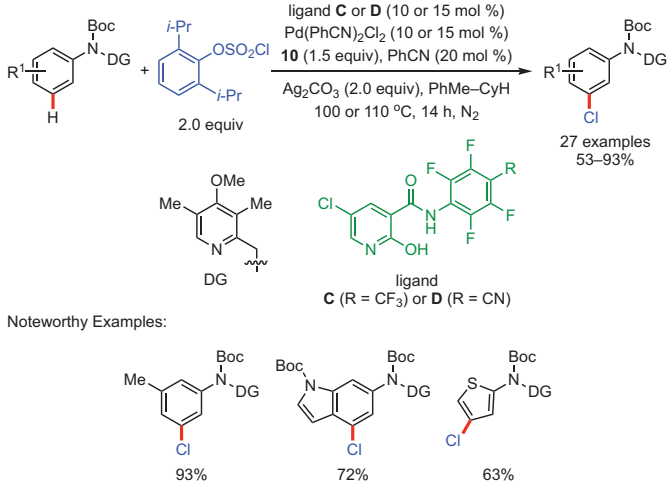
Scheme 4. *meta*-C–H Amination of Anilines and Phenols and Its Application in the Synthesis of a BRAF Inhibitor. *(Ref. 29)*

3.1.1. Olefination

Deng and Yu have developed a protocol for template-assisted *meta*-C–H olefination of phenylacetamides by using *N*-formyl-protected glycine (For-Gly-OH) as ligand and KH_2PO_4 as additive, both of which were crucial for the success of the reaction (**eq 10**).[32] A series of *meta*-olefinated phenylacetamides, some of which not readily available, were synthesized through this protocol. This report demonstrated that the benzonitrile directing group could accommodate different ring sizes of the macropalladacycle in the activation of the *meta*-C–H bonds of arenes. It should be noted that, in an earlier report, Maiti's group had also disclosed another nitrile-based directing group for the *meta*-C–H olefination of phenylacetic acids.[33] The first step in the proposed catalytic cycle involves *meta*-C–H activation of the substrate with Pd(II) through coordination with the CN group, generating a macropalladacycle. Coordination of the macropalladacycle with



eq 8 *(Ref. 29)*



eq 9 *(Ref. 30)*

the olefin results in a complex, which undergoes 1,2-migratory insertion followed by β-hydride elimination to release the *meta*-C–H functionalized product and a palladium hydride. Reductive elimination converts the palladium hydride into Pd(0) that is then reoxidized by the silver salt to Pd(II), which re-enters the catalytic cycle.

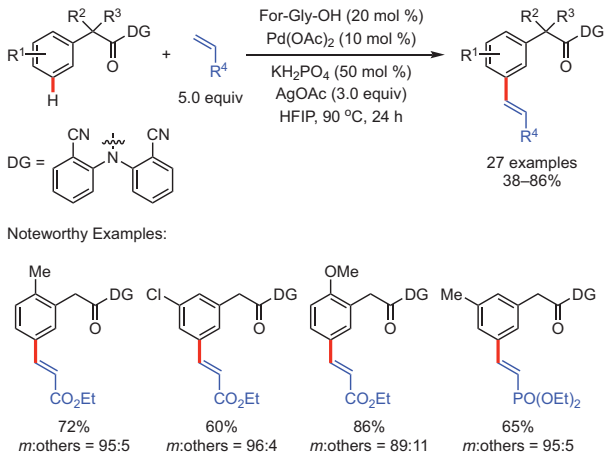
In the same year, Maiti and co-workers introduced a novel strategy for *meta*-selective mono-, di-, and sequential hetero-di-olefinations of benzylsulfonyl ester derivatives using 2-hydroxybenzonitrile as the directing group (**eq 11**).[34] This work is of great significance for the synthesis of divinylbenzene derivatives, which are an important class of molecular building blocks. The sulfonyl tether is helpful in achieving high *meta*-selectivity even for unbiased substrates. Moreover, the directing group is commercially available, simple to synthesize, and easy to remove.

Subsequently, our group reported a remote and selective *ortho*- and *meta*-C–H olefination of phenylethylamines—a key structural feature in a number of important drugs—through a regiodivergent functionalization protocol, which is promoted by a novel and simple 2-cyanobenzoyl group as the directing group. Tertiary amides undergo efficient *meta*-C–H olefination in the presence of $Pd(OAc)_2$ and Ac-Gly-OH under a nitrogen atmosphere (**eq 12**).[35] To demonstrate the potential of this approach for building complexity in a concise manner in the synthesis of highly substituted arenes, tetra-substituted phenylethylamide **13** was generated in 4 steps and 52% overall yield by sequential *ortho*- and *meta*-CHFs.

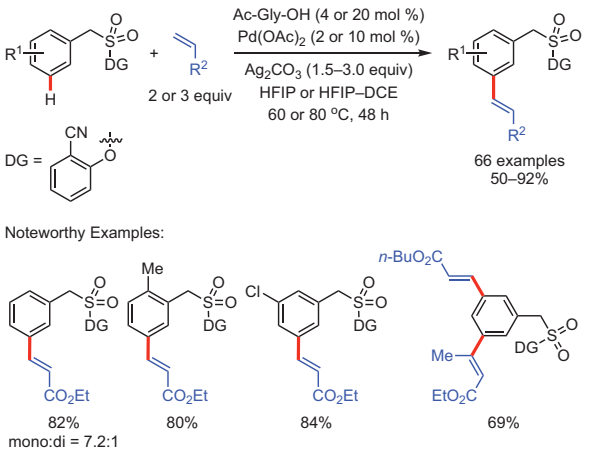
In early 2016, Maiti and co-workers reported the *meta*-selective mono-olefination and bis-olefination of benzylsilane derivatives by using 2-hydroxy-5-methoxybenzonitrile as the directing group.[36] Significantly, *meta*-olefinated toluene, benzaldehyde, and benzyl alcohol were obtained from the initial *meta*-olefination products under suitable desilylation conditions.

Although the chelation-assisted *meta*-CHF of electron-rich arenes had been reported,[11–14] the *meta*-C–H activation of electron-poor arenes such as benzoic acids or their derivatives via transition-metal catalysis had remained unsuccessful. In 2016, our group disclosed a palladium–catalyzed, *meta*-C–H olefination of electron-poor benzoic acid derivatives with a nosyl-protected 2-cyanophenylethylamine directing group (**eq 13**).[37] Notably, the new protocol introduced the environmentally benign molecular oxygen as the terminal oxidant in the presence of a catalytic amount of $Cu(OAc)_2$, which replaced the costly silver salt oxidants required in all previous chelation-assisted *meta*-C–H olefinations. Interestingly, a good ratio of mono over di-olefination was achieved by using For-Gly-OH instead of Ac-Gly-OH in the presence of the inorganic base KH_2PO_4. Moreover, the sulfonamide directing group, $2\text{-}NCC_6H_4(CH_2)_2NHNs$, can be prepared on a large scale from inexpensive starting materials, and can be easily cleaved under very mild conditions and recycled.

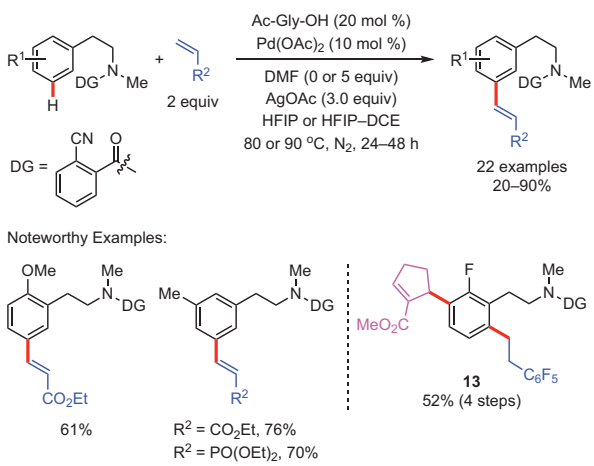
The first example of a room temperature *meta*-C–H olefination of arenes was disclosed by Maiti's group. The reaction is catalyzed by Pd(II), and a benzylic phosphonate ester is employed as the directing group (**eq 14**).[38] Remarkably, complete selectivity for the mono-olefinated arene was achieved, without any diolefinated product being observed. Moreover, the homo- and hetero-diolefinations at the *meta*-positions were achieved by raising the temperature to 80 °C in the presence of Ac-Gly-OH instead of Ac-Phe-OH ligand. Furthermore, the $-P(O)(OR)_2$ tether linkage could be readily transformed into alkene derivatives through a modified Horner–Wadsworth–Emmons reaction.



eq 10 *(Ref. 32)*



eq 11 *(Ref. 34)*



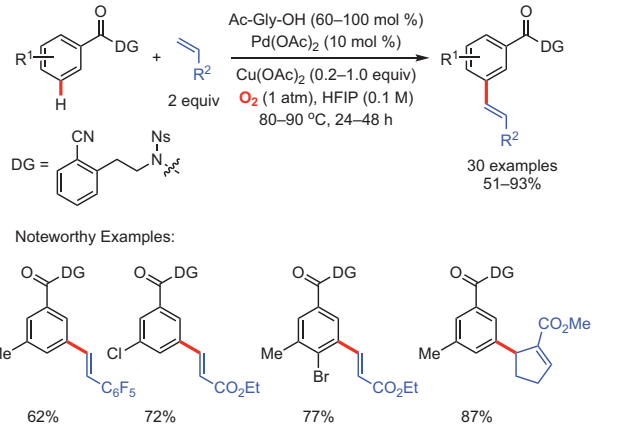
eq 12 *(Ref. 35)*

Maiti's group exploited further this template-assisted strategy in the palladium-catalyzed, selective *meta*-C–H olefination of 2-phenylethanesulfonic acid and 3-phenylpropanoic acid derivatives.[39] Sequential hetero- and homo-diolefinations were also achieved by using mono-olefinated 2-arylpropanoic acids as substrates, resulting in bis-*meta*-olefinated products. Mass spectrometric studies suggested the formation of a 12-membered cyclophane-like palladacycle in the reaction. Moreover, the cleavage and recovery of the directing template was successfully accomplished through a base-mediated hydrolysis process.

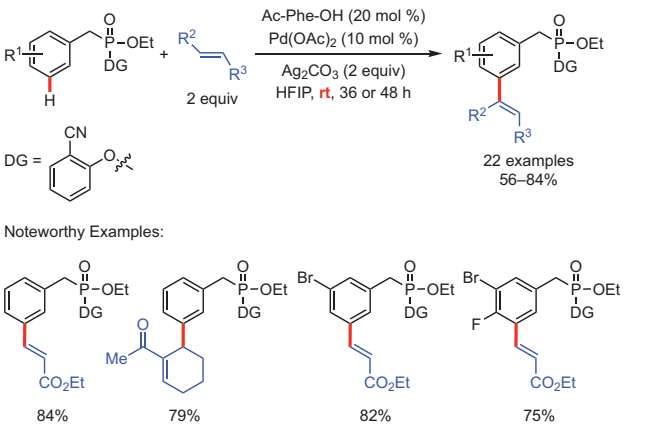
The same laboratory disclosed the distal C–H olefination of biphenylbenzoic acid and phenol derivatives with high regioselectivity (**eq 15**).[40] Some advantages of this approach are ease of scale-up and ease of cleavage and recovery of the directing group; one limitation, however, is that heterocyclic or appended naphthalene substrates could not be used. It should be mentioned that similar C–H olefinations of biphenyl derivatives had also been achieved previously by Yu's group.[31]

Carbon dioxide (CO_2) is an ideal reagent for carbamate synthesis owing to it being nontoxic, readily available, stable, and inexpensive.[41–44] In 2017, our group was the first to incorporate CO_2 into a novel, nitrile-containing directing group, **14**, for the purpose of *meta*-C–H activation of anilines (**Scheme 5**, Part (a)).[45] Under the optimal reaction conditions, a broad range of aniline derivatives were efficiently olefinated at the *meta*-position with $Pd(OAc)_2$ in good-to-excellent yields (Scheme 5, Part (b)). Moreover, the directing group could be easily cleaved under mild conditions, which would be advantageous in late-stage C–H functionalizations of complex molecules.

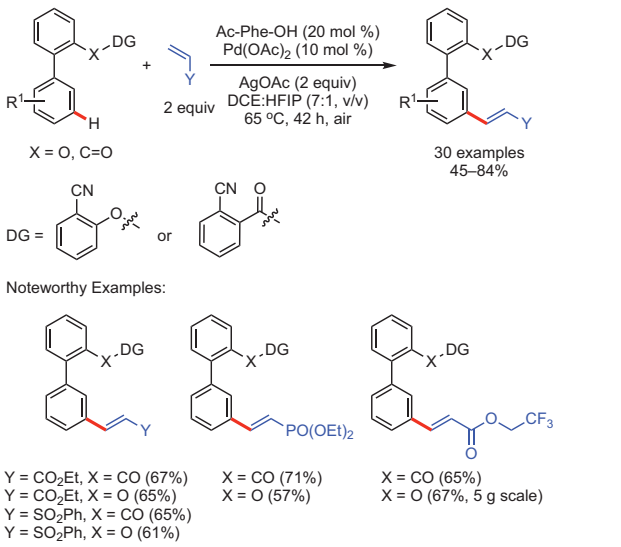
Very recently, Jin, Xu, and co-workers reported a highly regioselective and Pd-catalyzed remote *meta*-C–H olefination of distal arene-tethered alcohols assisted by a salicylonitrile template.[46] A variety of substrates, including 2-phenylethyl and 3-phenylpropyl alcohols and their long-chain homologues, were compatible with this



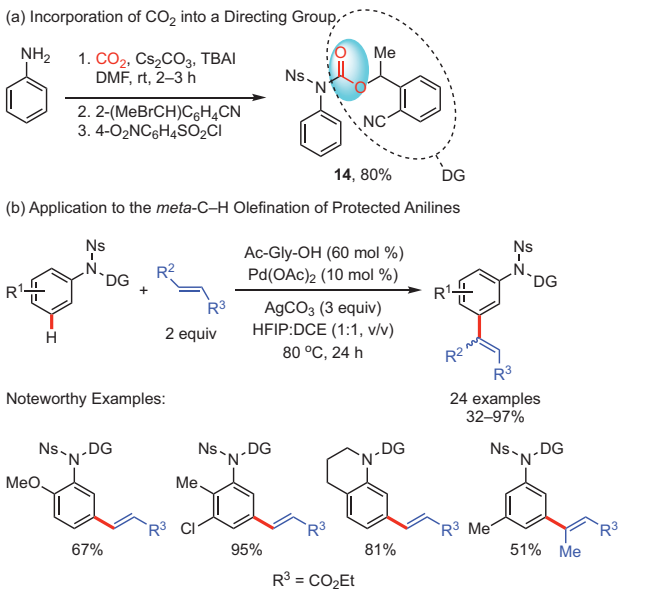
eq 13 *(Ref. 37)*



eq 14 *(Ref. 38)*



eq 15 *(Ref. 40)*



Scheme 5. (a) Incorporation of CO_2 into a Directing Group. (b) *meta*-C–H Olefination of Aniline Carbamates. *(Ref. 45)*

new protocol. It was suggested that both the C–N–Ag angle and gauche conformation of the phenyl ether in the macrocyclic transition state were the dominant factors for *meta*-selectivity, and this hypothesis was corroborated by a detailed computational study. The utility of this template in directing remote C–H activations was demonstrated in the case of two dipeptide substrates (**Scheme 6**).[46]

Simultaneously, Yu, Houk, and co-workers designed a conformationally flexible template for the *meta*-C–H olefination of benzoic acid derivatives guided by computational studies.[47] The newly designed template revealed that when the distance between the target C−H bond and the functional handle of the native substrate decreases, the templates can be lengthened to achieve *meta*-C–H selectivity. This work demonstrated that the combination of synthetic and computational chemistry might promote the development of novel templates for remotely and selectively activating C–H bonds. Interestingly, the new template used here is longer by one atom in the linkage when compared to the one disclosed by Li and co-workers for benzoic acid derivatives in an earlier report.[37]

3.1.2. Oxygenation

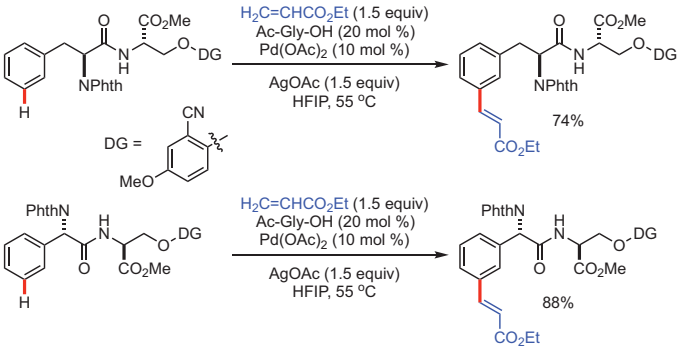
Another type of C–C bond forming reaction using a nitrile-based directing group is *meta*-C–H arylation,[48,49] which was published before 2015 and will not be covered here. The ability of the palladium-catalyzed, *meta*-C–H activation—assisted by a nitrile-based directing-group—to form carbon–heteroatom bonds was also explored and demonstrated by acetoxylation, hydroxylation, and the sole example of trifluoroethoxylation.[37,38,45,50–52] The new protocol proceeds via a Pd(II)/Pd(IV) redox cycle rather than the Pd(II)/Pd(0) catalytic cycle in other *meta*-C–H olefinations. The first remote *meta*-selective acetoxylation of aniline and benzylamine derivatives was achieved by Yu and co-workers in 2014.[50]

Subsequently, our group disclosed the *meta*-acetoxylation of electron-deficient benzoic acid derivatives by using the nosyl-protected 2-(2'-cyanophenyl)ethylamine as the directing group (**eq 16**).[37] Remarkably, the directing group in the resulting products could be easily cleaved under mild basic conditions to form several different and useful *meta*-functionalized entities containing a benzoic acid core.

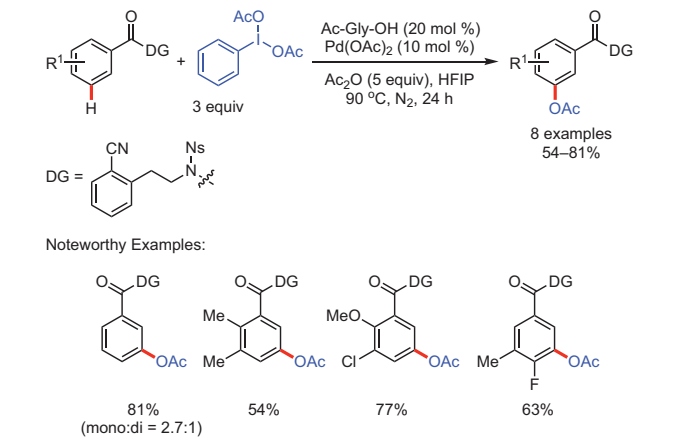
The palladium-catalyzed *meta*-C–H acetoxylation of benzylsulfonyl scaffolds using $PhI(OAc)_2$ as the acetoxylating reagent and Boc-Ala-OH as ligand has been reported.[51] Interestingly, a change of $PhI(OAc)_2$ to $PhI(TFA)_2$, with For-Gly-OH as ligand, led to *meta*-C–H hydroxylation instead of acetoxylation (**Scheme 7**).[51] This is likely due to the easier hydrolysis of the trifluoroacetate than the acetate intermediate under the reaction conditions. The synthetic utility of this approach was illustrated by concise syntheses of a resveratrol precursor and a phase II quinone reductase activity inducer.

The same laboratory successfully extended this methodology to the *meta*-C–H acetoxylation and hydroxylation of benzylic phosphonates by employing the same conditions and reagents.[38] The facile removal of the phophonate tether permitted the synthesis of 1,3- and 1,3,5-trialkenylarenes in good-to-high yields.

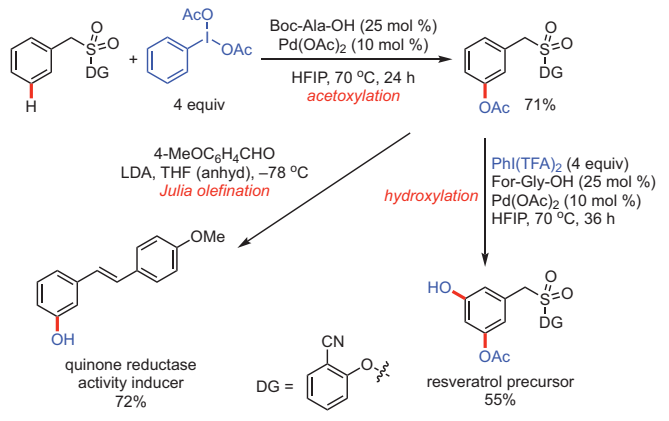
As discussed previously, our group incorporated CO_2 into a novel nitrile-containing directing group and achieved the successful *meta*-C–H olefination of anilines. We extended this methodology to the *meta*-C–H acetoxylation of unsubstituted and mono- and disubstituted protected anilines with $PhI(OAc)_2$ to afford the *meta*-acetoxylation products in moderate-to-good yields.[45] Moreover, very recently, our group successfully accomplished the first direct *meta*-C–H trifluoroethoxylation of an *N*-sulfonylbenzamide en route to a formal synthesis of flecainide, a drug that is used to prevent and treat tachyarrhythmias (**Scheme 8**).[52] This approach should be important in medicinal chemistry and drug discovery, since it is potentially



Scheme 6. Application of Jin and Xu's Remote *meta*-C–H Activation of Distal Arene-Tethered Alcohols. *(Ref. 46)*



eq 16 *(Ref. 37)*



Scheme 7. Application of Maiti's *meta*-C–H Acetoxylation and Hydroxylation of Benzylsulfonyl Scaffolds. *(Ref. 51)*

applicable to the synthesis of flecainide derivatives bearing other substituents on the benzene ring, which is difficult to achieve by the known methods.

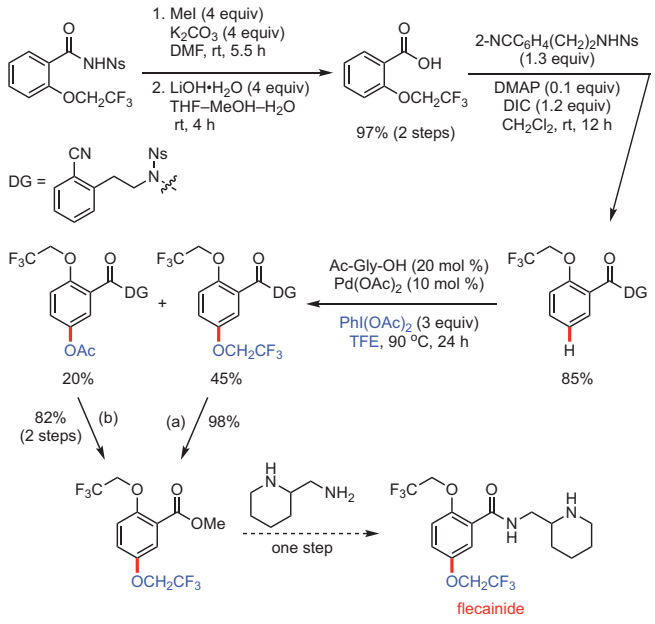
3.1.3. Silylation and Germanylation

Since silicon functional groups can be easily converted into versatile functionality,[53–56] a selective one-step *meta*-C–H silylation reaction was long overdue. Maiti and co-workers disclosed the first report of such a transformation in 2017, employing a pair of polysubstituted benzonitriles as directing groups and hexamethyldisilane as the silylating reagent (**eq 17**).[57] Benzylsulfonate esters and other arylalkanesulfonate esters were compatible with this protocol by overcoming the large strain energy associated with formation of a metallacycle intermediate possessing a greater-than-11-membered ring. In addition, *meta*-germanylation of benzylsulfonates was also achieved in moderate yields and with excellent selectivity in spite of the higher reducing property of the digermanium reagent and lower stability of the C−Ge bond. The synthetic utility of this new *meta*-C–H silylation was demonstrated in a formal synthesis of TAC101, a potential drug candidate for the treatment of lung cancer.

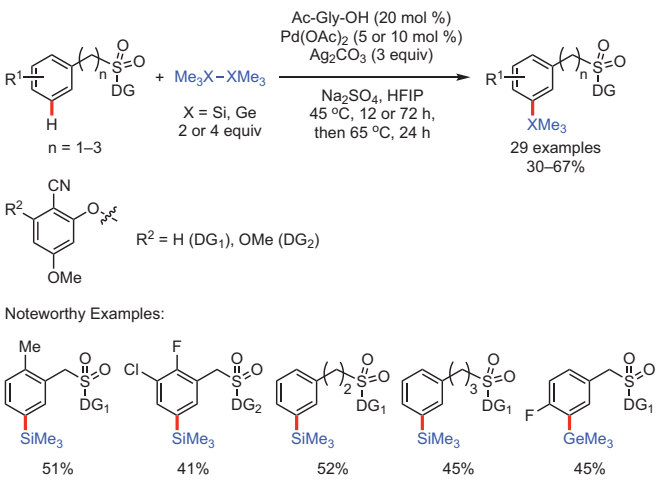
3.2. *meta*-C–H Functionalization Assisted by an N-Heterocycle-Containing Directing Group

In an effort to amplify on existing remote *meta*-C–H functionalizations, Yu and co-workers developed a new directing group in which the weakly coordinating nitrile group was replaced with a pyridyl group—a strongly coordinating *ortho*-directing group. Through molecular design based on distance and geometry, this group was engineered to direct the *meta*-C–H olefination and iodination of benzyl and phenylethyl alcohols.[58] This new protocol demonstrated that the pyridyl group not only maintained the U-shaped conformation, but also mimicked the end-on coordination, which paved the way for developing various unexplored *meta*-C–H transformations. In this way, a new *meta*-C–H iodination reaction was realized using 2-fluoropyridine as the directing group and DIH (1,3-diiodo-5,5-dimethylhydantoin) as the iodination reagent, affording aryl iodides in good yields (**eq 18**).[58] Such aryl iodides can serve as reaction partners in a wide range of carbon–carbon and carbon–heteroatom bond-forming reactions such as the Heck and Suzuki cross-coupling reactions. This *meta*-iodination reaction had not been possible using nitrile-based directing groups.

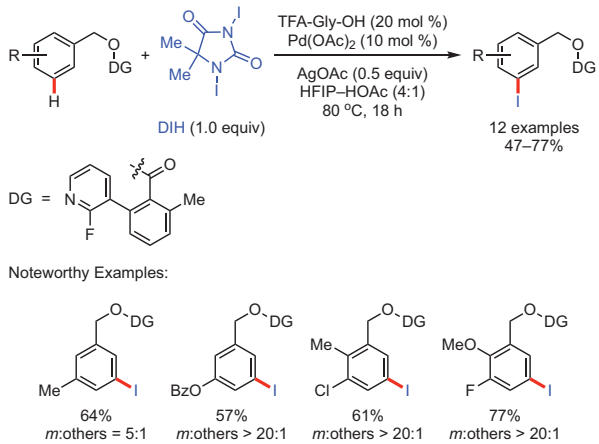
A novel, biphenylpyrimidine-based directing template has very recently been employed to effect the selective, palladium-catalyzed *meta*-C–H alkylation and alkenylation with allylic alcohols. Benzylsulfonyl, benzylphosphonate, phenethylcarbonyl, and phenethylsulfonyl ester scaffolds were successfully functionalized at the meta position, leading to the formation of β-aryl aldehydes and ketones (**eq 19**).[59] It is worth noting that the nitrile-group-directed *meta*-C–H activation had not been reported with an allyl alcohol. Additionally, this protocol permitted for



Scheme 8. The First Reported *meta*-C–H Trifluoroethoxylation of an Arene en Route to a Formal Synthesis of the Antiarrhythmic Agent, Felcainide. *(Ref. 52)*



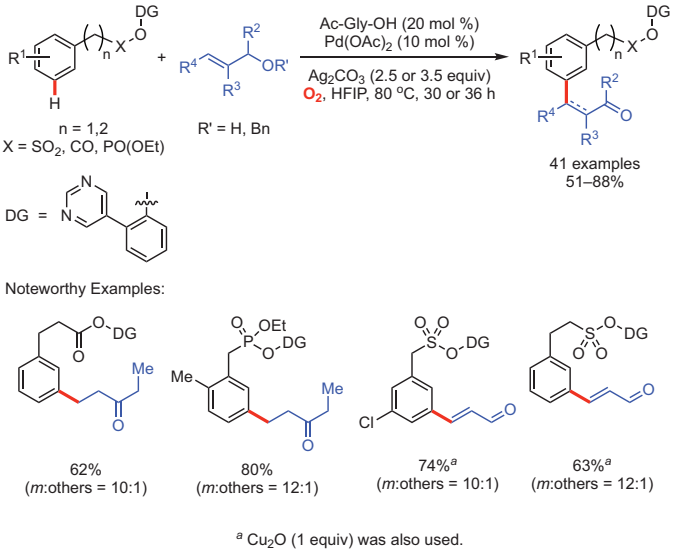
eq 17 *(Ref. 57)*



eq 18 *(Ref. 58)*

the first time the generation of α,β-unsaturated aldehydes by in situ removal of the benzyl group from the benzyl-protected allyl alcohol alkenylating partner.

Although the U-shaped-template-assisted *meta*-C–H bond activation through a macrocyclic cyclophane transition state has been improved by expanding its scope and efficiency, it is still limited by the need for an appropriate functional group to covalently attach the template to the substrate and by the incompatibility of most heterocyclic substrates with this approach. To overcome these limitations, Yu and co-workers reported very recently a remote *meta*-C–H olefination of 3-phenylpyridines by using a *catalytic amount* of a well-designed bifunctional template in the presence of both $Pd(OAc)_2$ and $Cu(OAc)_2$ *without attaching the template to the substrates* (**eq 20**).[60] This catalytic pyridine-containing sulfonamide template with two metal coordination centers binds the heterocyclic substrates via a reversible coordination instead of a covalent linkage. In this way, a stoichiometric amount of a covalently attached template was not required for this challenging *meta*-C–H olefination of pyridine derivatives.

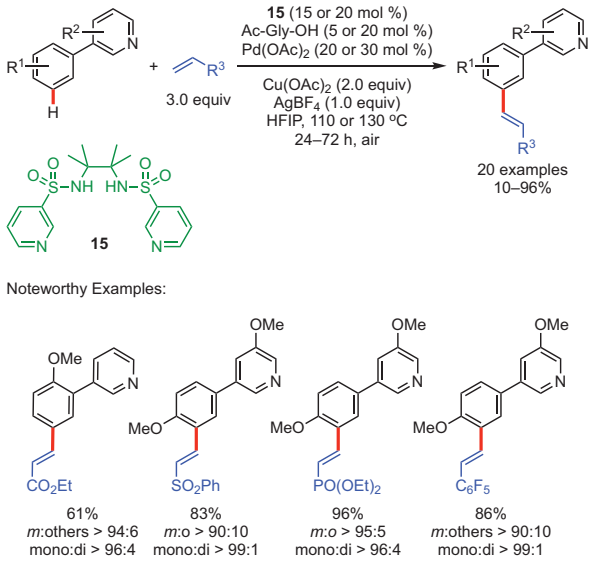


eq 19 *(Ref. 59)*

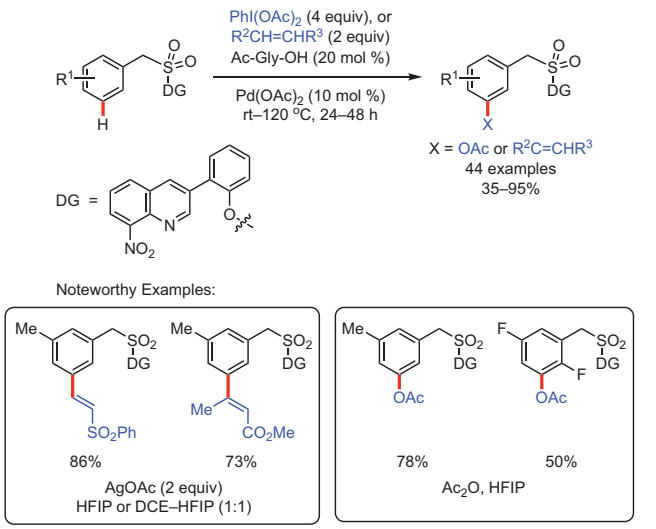
Although σ-coordination of a heteroatom-containing directing group has been extensively utilized in directed *ortho*-C–H functionalizations and aliphatic C–H activations,[61,62] selective *meta*-C–H functionalizations using strong σ-coordination has remained a great challenge. In this regard, Maiti and co-workers have introduced 8-nitroquinoline as the directing group that forms a stable palladacycle leading to selective *meta*-olefination and *meta*-acetoxylation of sulfonates (**eq 21**).[63] This palladium-catalyzed, sulfonate-linked, and 8-nitroquinoline-based *meta*-C–H functionalization mimicks the traditional *ortho*-C–H functionalization through strong σ-coordination. The *meta*-olefinated and acetoxylated arenes thus produced were further elaborated into a variety of valuable compounds some of which are difficult to synthesize by other methods. The versatility and attractiveness of this *meta*-olefination protocol was demonstrated in a high-yield (86%), gram-scale synthesis.

4. Remote *para*-C–H Functionalization Assisted by a *para*-Directing Group

Several successful outcomes have been achieved in the selective *para*-C–H activation over the past few years.[15] However, the traditional strategies for *para*-C–H functionalization are governed either by electronic factors or steric demands and suffer from lower yields, narrow substrate scopes, and poor regioselectivity. While the directing-group–assisted and palladium-catalyzed *meta*-C–H bond functionalizations have become a class of relatively mature transformations, few reports exist on the selective functionalization of the *para*-position that utilizes a template strategy. Thus, achieving the *para*-C–H functionalization with good selectivity and yields has remained problematic and extremely challenging.



eq 20 *(Ref. 60)*



eq 21 *(Ref. 63)*

In 2015, Maiti and co-workers published the first report on the remote *para*-C–H functionalization of arenes using a novel, systematically engineered, silicon-containing, and biphenyl-based template that directs the remote functionalization by forming a D-shaped assembly.[64] Moreover, *ortho*- and/or *meta*-C–H activation would be highly disfavored owing to the rigidity of the biphenyl moiety. The utilization of a di-isopropyl-substituted silyl center as the tether was essential to the *para*-selective functionalization, since the presence of two sterically hindered isopropyl groups at silicon leads to a "Thorpe–Ingold" effect, which allows the coordinating nitrile group to get closer to the *para*-C–H bond by a domino-like "steric push" (**eq 22**).[64]

This new protocol is compatible with a broad range of olefinic partners and arene substrates possessing either electron-donating or electron-withdrawing groups, and affords *para*-olefinated products in satisfactory yields and good-to-excellent *para*-selectivity. This template-assisted strategy was extended to the regioselective *para*-acetoxylation of toluene derivatives in moderate yields. Moreover, the cyanobiphenylol directing group can be easily cleaved from the products and recovered with either tetrabutylammonium fluoride (TBAF) or *para*-toluenesulfonic acid (PTSA).

In 2016, Maiti and and co-workers revisited their work on the palladium-catalyzed *para*-C–H functionalization by switching the positions of the benzylic methylene and phenolic oxygen atom in the substrate and directing group, respectively, resulting in a modified template for the *para*-C–H olefination of phenol derivatives (**eq 23**).[65] This protocol tolerated not only a wide range of electron-donating and electron-withdrawing substituents, but also a diverse array of olefins including esters, aldehydes, amides, ketones, phosphonates, sulfonyls, and olefins with long-chain alkyl substituents. The usefulness of this *para*-functionalization reaction was demonstrated by applying it to the synthesis of various phenol-based natural products and complex molecules—such as drupanin, artepillin, plicatin B, ferulic acid, dehydrozingerone, fenchyl 4-hydroxycinnamate, and *para*-coumaric acid—in good-to-excellent yields.

5. Conclusion and Outlook

The past few years have witnessed rapid developments in palladium-catalyzed *meta*- and *para*-C–H bond functionalizations assisted by a chelating directing group. Strikingly, the innovative palladium(II)–norbornene relay approach has evolved rapidly to effect a series of unprecedented *meta*-C–H bond transformations by employing novel ligand scaffolds and modified transient mediators (2-carbomethoxynorbornene). New types of "end-on" coordinating templates have been engineered to expand the scope of *meta*-C–H bond functionalization reactions, and *para*-C–H bond transformations have been accomplished by designing novel D-shaped templates. These improvements will open up new avenues for expediting access to specialized molecules. Despite these significant advances, there remains a strong need to expand the types of transformation possible as well as the substrate scopes of existing methods. For application on a large scale, significant efforts are still required to improve the current protocols, such as by lowering the catalyst loading and simplifying the template. Finally, a more promising and efficient way to achieve the desired regioselectivity would be to use a catalytic amount of a detached directing group, or to install the directing functionality on a suitable ligand that is also capable of promoting the reactivity of metal catalysts required for activating the target C–H bond.

6. Acknowledgment

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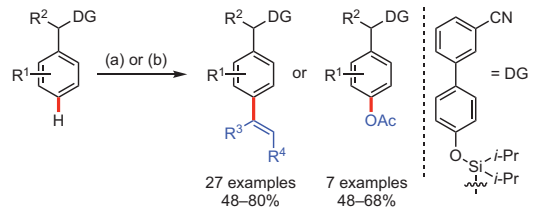
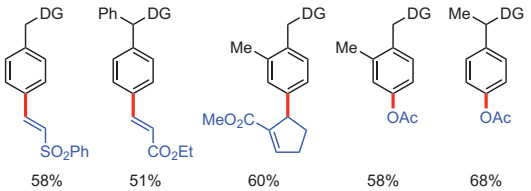
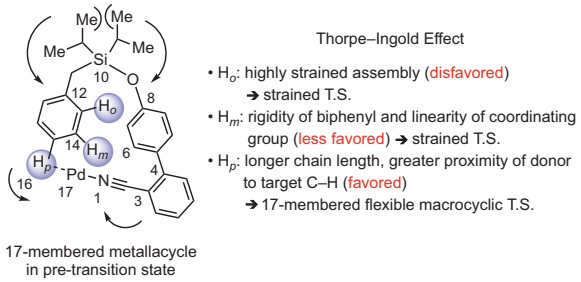
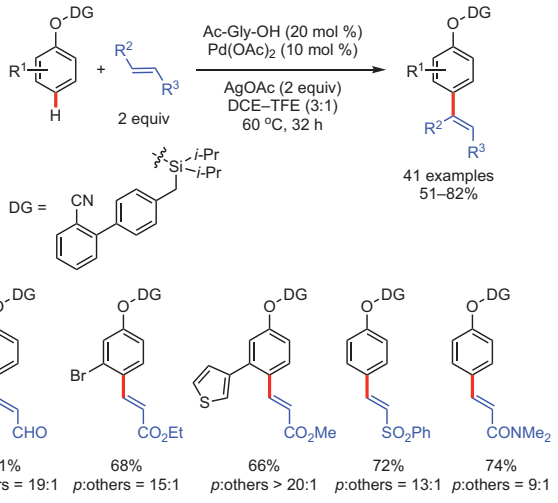


(a) $R^3HC{=}CHR^4$ (2 equiv), Ac-Phe-OH (20 mol %), $Pd(OAc)_2$ (10 mol %), AgOAc (3 equiv), HFIP, 90 °C, 36 h.
(b) $PhI(OAc)_2$ (2 equiv), Piv-Ala-OH (30 mol %), $Pd(OAc)_2$ (15 mol %), HFIP, 70 °C, 24 h.





eq 22 *(Ref. 64)*



eq 23 *(Ref. 65)*

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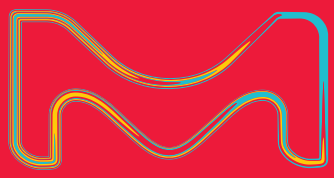

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