ChemComm

ROYAL SOCIETY OF CHEMISTRY

FEATURE ARTICLE

View Article Online
View Journal



Cite this: DOI: 10.1039/d0cc04863a

# Traceless directing groups: a novel strategy in regiodivergent C–H functionalization

Geetika Rani, Vijay Luxami and Kamaldeep Paul *

The use of functional groups as internal ligands for assisting C–H functionalization, termed the chelation assisted strategy, is emerging as one of the most powerful tools for construction of C–C and C–X bonds from inert C–H bonds. However, there are various directing groups which cannot be either removed after functionalization or require some additional steps or reagents for their removal, thereby limiting the scope of structural diversity of the products, and the step and atom economy of the system. These limitations are overcome by the use of the traceless directing group (TDG) strategy wherein functionalization of the substrate and removal of the directing group can be carried out in a one pot fashion. Traceless directing groups serve as the most ideal chelation assisted strategy with a high degree of reactivity and selectivity without any requirement for additional steps for their removal. The present review overviews the use of various functional groups such as carboxylic acids, aldehydes, *N*-oxides, nitrones, *N*-nitroso amines, amides, sulfoxonium ylides and silicon tethered directing groups for assisting transition metal catalyzed C–H functionalization reactions in the last decade.

Received 15th July 2020,
Accepted 20th August 2020

DOI: 10.1039/d0cc04863a

rsc.li/chemcomm



## 1 Introduction

C–H activation has emerged as one of the most attractive practical strategies for the reliable construction of C–C and C–X bonds.[1–10] This approach aids in achieving the fundamental aim of building molecular complexes from readily available and simple hydrocarbon counterparts.[11] In contrast to the limited scope and byproduct formation in coupling reactions, C–H activation enables a broad substrate scope by the virtue of C–H bonds. The ubiquitous nature of C–H bonds, besides negating the need for pre-functionalization of the starting substrate, however, exhibits an inherent limitation to achieve selectivity for specific C–H bonds within the chemically homogeneous environment of a molecule.[12]

*School of Chemistry and Biochemistry, Thapar Institute of Engineering and Technology, Patiala-147001, India. E-mail: kpaul@thapar.edu*

**Geetika Rani**

*Ms Geetika Rani is working as a Junior Research Fellow (JRF) under the supervision of Dr Kamaldeep Paul in the School of Chemistry and Biochemistry, TIET, Patiala, India. She has pursued her Master's from PAU, Ludhiana, India. She is mainly interested in the design and synthesis of novel organic molecules of medicinal uses by transition metal catalyzed C–H activation.*

**Vijay Luxami**

*Vijay Luxami received her PhD from Department of Chemistry, Guru Nanak Dev University Amritsar. She joined the School of Chemistry and Biochemistry, Thapar Institute of Engineering and Technology, Patiala, as an Assistant Professor in 2010. She has received various awards like DST Young Scientist, DST INSPIRE Faculty, DST-DFG awards etc. She has worked as a visiting scientist at University of Bath, UK. She has 75 research publications in SCI journals. Currently, she is working as an Associate Professor at TIET, Patiala. Her area of research is organic supramolecular materials and their applications in molecular electronics.*

This could be solved by application of the innate reactivity of a molecule, which involves using the nucleophilicity/acidity of the molecule to dictate functionalization at a specific site.[13] Another viable strategy is installment of a functional group moiety on the molecule[14] that plays the role of an internal ligand coordinating to the metal center, thereby bringing the metal catalyst into close proximity to a specific C–H bond.[15] This ensures selective C–H bond functionalization with accelerated reactivity and a high degree of regioselectivity. The functional groups, besides enhancing the selectivity and reactivity at proximal positions, also have the ability to serve the same function at distal positions in certain cases.[16–24] This type of exceptional behavior where directing groups assist in achieving distal effects is called distal C–H functionalization.[25–28]

Directing groups, however, have been diverse in terms of their approaching action. (i) The first class of directing groups (referred to as non-removable directing groups) remain as a substantial part of the product or undergo cyclization to form another heterocyclic moiety and therefore it is difficult to remove them after functionalization.[29] But since these ligands are not part of the target scaffolds, it becomes a highly challenging task to extrude them as a structural functional moiety. (ii) The second class of directing groups (termed removable directing groups) includes groups which could be removed or modified after functionalization.[30–37] However, this removal or modification requires additional steps and therefore it limits the cost and atom economy of the strategy on an industrial scale. A viable solution to this was (iii) the third class of directing groups (termed transient directing groups), which coordinate themselves to any pre-existing moiety (say X) in the molecule and get released after placing functionalization.[38–46] Although significant contributions in the development of these groups were made, there were somehow limitations owing to the drawback of the pre-requisite presence of some unstable functional moieties to which the transient directing group could tether reversibly, *e.g.* reversible formation of phosphinites, imines and enamine functionalities.[47] (iv) A novel class of directing groups is termed traceless directing groups (TDGs), where functional groups inherent to a number of naturally and commercially available compounds assist in carrying out transformations with their subsequent removal from the functionalized moiety in one pot (Fig. 1). There is a very thin line of difference between transient and traceless directing groups. The former need additional steps for installation, while the latter are inherent to a variety of compounds. Moreover, transient directing groups need some functional moiety inherent to the compounds to which the directing groups could tether themselves.[13,48] C–H functionalization with traceless directing group gained high momentum in 2008 after the pioneering work of Satoh and Miura where carboxylic acid served as a traceless directing group in Pd-catalyzed vinylation of indole and other heterocyclic skeletons.[49] Thereafter, several elegant studies have been reported using some functionalities such as carboxylic acids, aldehydes, imines, nitroso, sulfoxonium *etc.* for directing C–H functionalization in a traceless manner.

Although functional groups which can be employed as traceless directing groups are still rare, there have been numerous literature reports on the use of traceless functional groups for metal directed C–H functionalization in the last decade. Thus, exploring the application of this novel strategy for C–H functionalization is highly desirable at the current stage. There have been some literature reports available on this chelation assisted strategy but they remain restricted to some selective transformations, transition metals or functional groups. A few reviews have been reported about specific traceless directing groups and discussed particularly carboxylic groups.[13,50] Although the majority of the literature reports on traceless directing groups appeared in the past several years, to the best of our knowledge there is no detailed literature survey of traceless directing groups other than carboxylic acid. Therefore, we felt the urgent need for a comprehensive review on this topic. This review will focus mainly on summarization of the current state of our knowledge about assisted functionalization of inert C–H bonds by various traceless directing groups.

**Kamaldeep Paul**

*Dr Kamaldeep Paul received his Master degree from Department of Pharmaceutical Sciences in 2000, and PhD in Synthetic Organic and Medicinal Chemistry from Department of Chemistry, Guru Nanak Dev University, Amritsar, in 2006. He is working as an Associate Professor in the School of Chemistry and Biochemistry, Thapar Institute of Engineering & Technology, Patiala, India. His area of research is Synthetic Organic and Medicinal Chemistry where his research is broadly focused on multistep synthesis of heterocyclic molecules, C–H functionalization and their in vitro evaluation for anticancer and antimicrobial activities.*

## 2 Classification of traceless directing groups

Generally, directing groups should have some criteria to achieve an effective traceless character: (i) during functionalization, the directing group should be regarded as stable and reversibly coordinated with the metal center, (ii) the directing group should assist C–H functionalization and thereafter be removed in a single step and (iii) the directing group should not constitute a part of the target molecule.

Some of the well-known traceless directing groups employed for C–H functionalization are carboxylic acids, carbon dioxide, aldehydes, silicon tethered groups, amide based groups, *N*-oxides, nitroso and α-imino oxy acids. The aim of this review is to present the summarized form of these traceless directing groups. To present in the best possible way, the review is divided into different functional groups employed as traceless directing groups in various

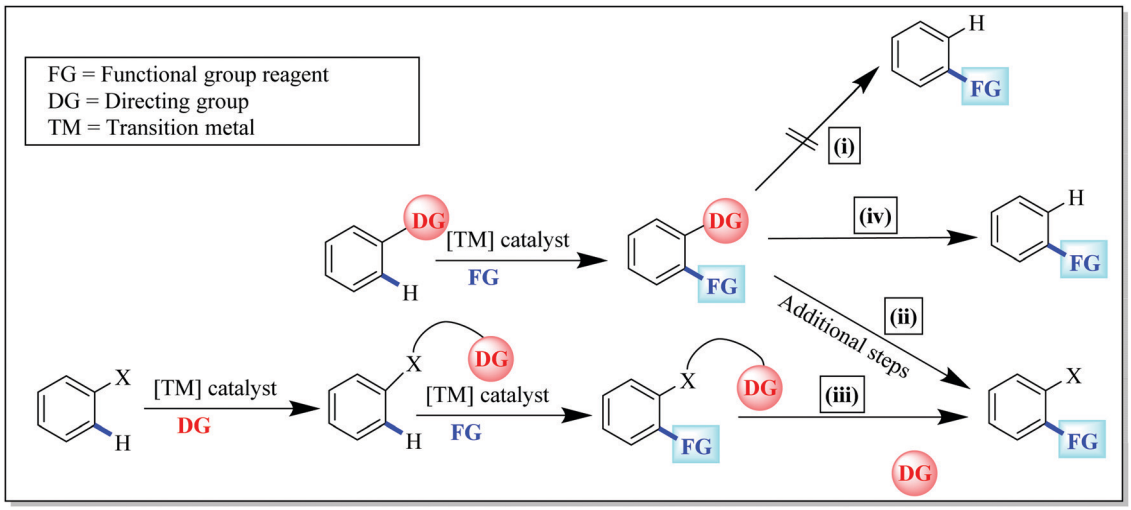



Fig. 1 Directing group strategies for C–H functionalization reactions. (i) Non-removable directing group strategy; (ii) removable directing group strategy; (iii) transient directing group strategy and (iv) traceless directing group (TDG) strategy.

categories *viz.*, (i) carbonyl groups, (ii) N–O groups, (iii) N–N groups, (iv) bidentate amides, (v) S–O groups, and (vi) Si based and other traceless directing groups.

## 2.1 Carbonyl group based traceless directing groups

**2.1.1 Carboxylic acid as a traceless directing group.** Carboxylic acid was amongst the first directing groups employed in the traceless approach of C–H functionalization. The use of carboxylic acids as traceless DGs involves sequential functionalization/decarboxylation of acids. This functionalization and decarboxylation may occur in a single step involving (i) a multi-catalyst system to catalyze both the sequential reactions or (ii) a single metal catalyst to serve in the process of catalysis of both reactions involved in the transformation. It may also involve (iii) *in situ* two step processes in which a metal catalyst assists in activation directed by intact carboxylic groups in the first step followed by protodecarboxylation catalyzed by another catalyst in a subsequent step (Fig. 2).

The use of carboxylic acids in directing transition metal catalyzed traceless C–H functionalization has grown rapidly in 2007 after the pioneering work of Dauglis and his co-workers.[51] This group carried out palladium (Pd) catalyzed direct *ortho*-arylation of benzoic acids with electronically diverse aryl iodides and chlorides. Soon after the arylation, Goossen and his co-workers illustrated both silver and copper catalyzed protodecarboxylation strategies.[52,53] In one of these illustrations, Pd catalyzed *ortho* coupling of 4-toluic acid and 1-iodo-3,5-bis(trifluoromethyl)benzene was carried out using silver acetate for protodecarboxylation. The reaction yielded the desired biaryl product with 51% yield and this illustration served as a blueprint for all the *ipso*-decarboxylative C–H functionalization reactions as it was the first successful demonstration of the traceless nature of carboxylic acid directing groups.

In 2008, Miura and his co-workers carried out Pd catalyzed regioselective vinylation of indoles (**1**) and related heteroatomic rings with alkenes at an unusual position directed by carboxylic groups (Scheme 1). The reaction involved two metal catalysts in a single step process where $Pd(OAc)_2$ catalyses both vinylation and decarboxylation and $Cu(OAc)_2$ serves as an oxidant. It was observed that LiOAc caused almost double the yield and one of the possible functions that were illustrated for its use is to provide acetate anions as ligands. This vinylation followed by decarboxylation is due to the coordination of $Pd(OAc)_2$ to the carboxylic group of the heterocyclic moiety and forms a Pd(II) carboxylate. Subsequently, it forms a palladacycle intermediate by directed palladation at the C2 position and further insertion of an alkene and elimination of β-hydride occur, finally forming hydridopalladium carboxylate. Then, it undergoes decarboxylation followed by reductive elimination affording 2-vinyl derivatives (**1a–h**).[49]

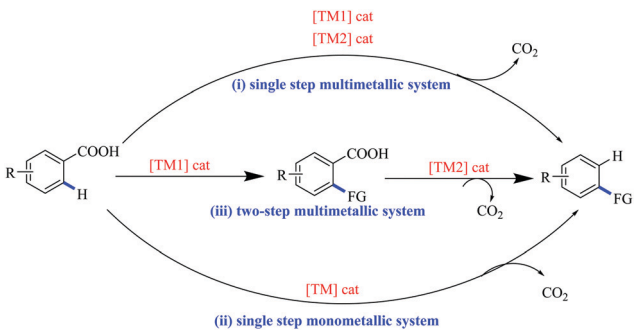
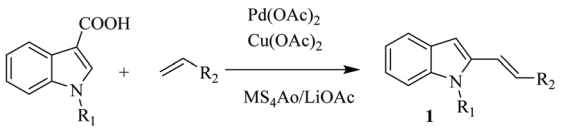
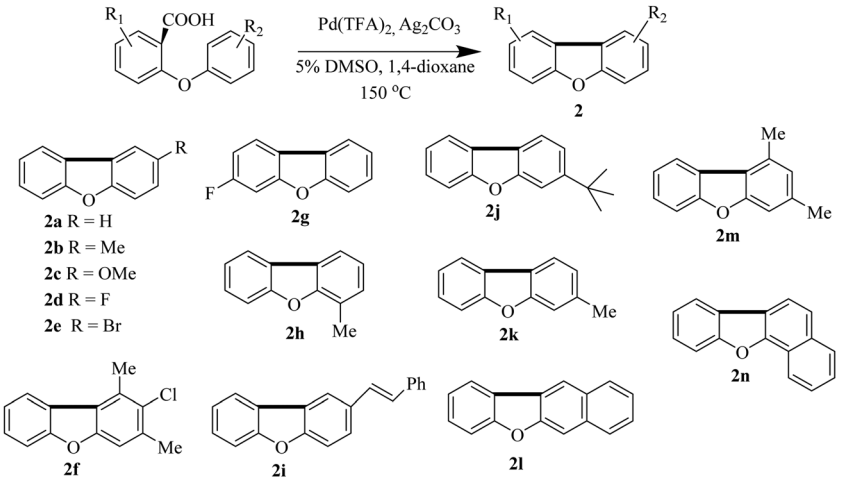



Fig. 2 Three methods of transition metal catalyzed C–H functionalization directed by carboxylic acids.



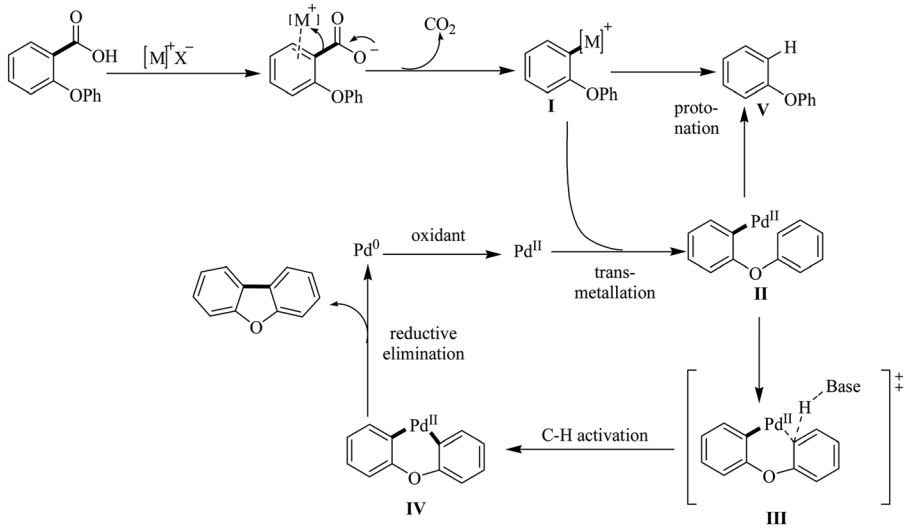

Scheme 1 Pd-Catalyzed vinylation of indoles.




Scheme 2 Intramolecular arylation of 2-phenoxy benzoic acid for dibenzofuran formation.

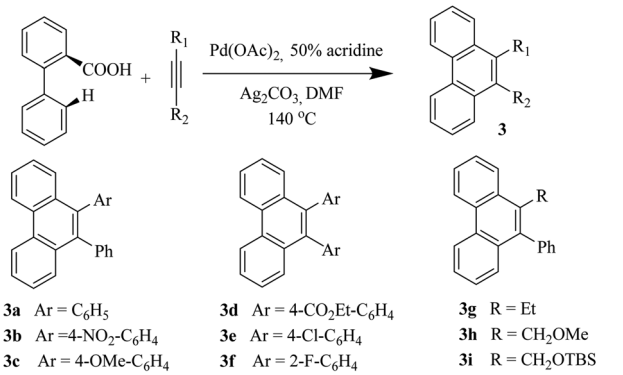
In 2009, Glorius and his co-workers developed a novel protocol for intramolecular arylation of 2-phenoxy benzoic acid to form dibenzofurans **2** (Scheme 2).[54] It proceeded through a highly selective decarboxylative C–H activation reaction carried out with $Pd(TFA)_2$ as a catalyst and silver carbonate as an additive. It was reported that a variety of dibenzofurans could be synthesized through this method. It was observed that when the same reaction was done with 2-phenoxy benzoic acids having electron-donating and electron-withdrawing substituents, it afforded the corresponding cyclized product through the formation of a palladacycle intermediate by intramolecular C–H activation (Scheme 3). The reaction proceeded through decarboxylation mediated by silver carbonate forming metal aryl species followed by transmetalation with $Pd(TFA)_2$ to form aryl palladium intermediate **II**, which further forms palladacycle intermediate **IV** through intramolecular C–H activation. This intermediate so formed undergoes reductive elimination to form the corresponding dibenzofuran species with Pd(0), which gets oxidized to regenerate the Pd(II) species. The Ag salt not only assists in decarboxylation but also serves as an oxidant for C–H activation. While the protonation of **I** and **II** to form **V** represents an undesired reaction to form the un-cyclized ether product, suppressing this step remains a challenge during the reaction.

In another approach, Glorius and co-workers extended their contribution towards traceless directing groups with alkynes. They developed a novel procedure for a Pd catalyzed intermolecular annulation reaction of 2-phenyl benzoic acids with various alkynes. The formal [4+2] annulations proceeded with sequential cleavage of both C–H and C–C bonds and resulted in the selective formation of phenanthridines (**3**) in moderate to good yields (Scheme 4).[55] The reaction was illustrated with two different mechanisms. In one of the mechanisms, alkynes form vinyl palladium species by carbometalation followed by intramolecular C–H activation and reductive elimination successively. In another mechanism, the acid substrate may undergo C–H activation followed by decarboxylation and reductive elimination.

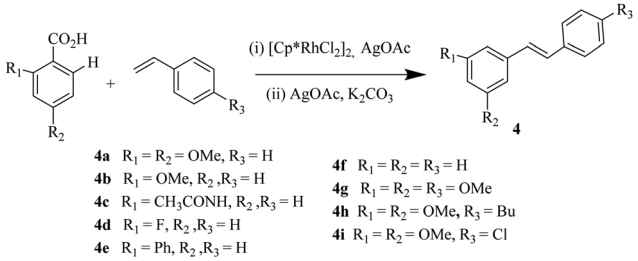



Scheme 3 Plausible reaction mechanism for intramolecular arylation of 2-phenoxybenzoic acids.




Scheme 4 Intermolecular [4+2] annulations of phenyl benzoic acids with alkynes.




Scheme 5 Synthesis of a series of *meta*-substituted stilbenes.

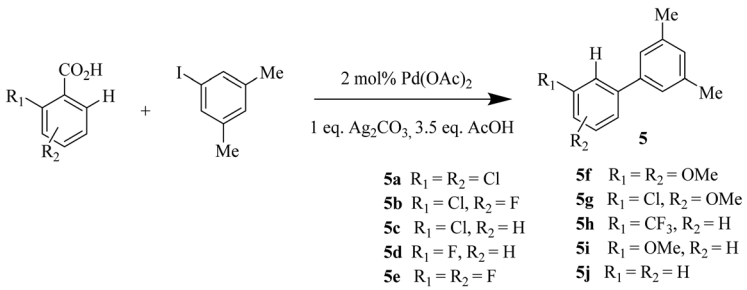
Miura and co-workers extended further the scope of metal catalyzed decarboxylative C–H olefination of benzoic acids with substituted styrene (Scheme 5).[56] They carried out a regioselective synthesis of a series of *meta*-substituted stilbenes (**4a–i**) from *ortho*-substituted benzoic acids. The olefination of *ortho*-substituted benzoic acids upon treatment with styrenes proceeded efficiently through an ordered decarboxylation reaction in the presence of a Rh(III) catalyst and silver acetate as an oxidant. The reaction occurred through 2 steps, a multi-catalyst mechanism. In the first step, it occurs through Rh catalyzed *ortho* olefination, followed by decarboxylation, where AgOAc served as an oxidant in the first step and a catalyst for decarboxylation in the other step.

Larossa and co-workers also attempted traceless carboxylic acid group directed formal arylation. It was the first example of *meta*-selective direct arylation with iodoarenes using carboxylic acid as a traceless directing group. The scope of the reaction was further envisaged by using substituted iodoarenes with F, Cl, Me, Br and $CO_2Me$ at the *para*- and *meta*-positions (**5a–j**). It was observed that decarboxylation was compatible with this wide range of *meta*-substituents (Scheme 6).[57] This approach was highly appreciated due to its exquisite control over the regioselectivity for the protodecarboxylation step and could replace highly expensive Suzuki couplings for the synthesis of biaryls.

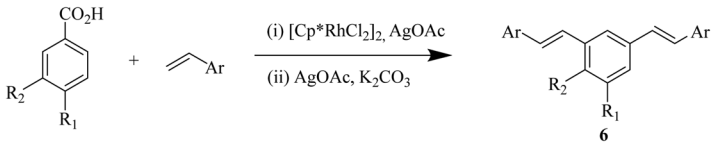
Miura and co-workers expanded his study on the synthesis of vinyl arenes through a decarboxylative mechanism in his previous analogous publication. They reported rhodium catalyzed olefination of substituted benzoic acids, α,β-unsaturated carboxylic acids, naphthoic acids, and heteroarene carboxylic acids with alkenes regioselectively at neighboring positions followed by decarboxylation to selectively produce the corresponding vinyl-heteroarene analogues (**6a–n**) (Scheme 7).[58] Here, the carboxylic oxygen coordinates to the metal giving rhodium(III) benzoate, which subsequently forms a rhodacycle intermediate *via ortho* rhodation. The intermediate then undergoes styrene coordination, migratory insertion and β-hydrogen elimination to enable the formation of the mono-olefinated product followed by a second olefination through the same mechanism.

In 2013, Larrosa and co-workers realized that it is difficult to synthesize the *ortho*-substituted benzoic acid overriding the protodecarboxylation process. They developed a practical strategy to synthesize 2-aryl-6-substituted benzoic acid derivatives (**7a–j**) by switching off the decarboxylation process (Scheme 8).[59] They realized that in this reaction $K_2CO_3$ plays a pivotal role in switching off the protodecarboxylation by overriding the challenging electronic and steric bias of the substrates. Thus, the carboxyl group remained intact after directed functionalization. However, earlier, when the reaction was carried out by them under the same conditions, but an extra equivalent of $Ag_2CO_3$ was used instead of using $K_2CO_3$, it was accompanied by tandem decarboxylation in the same pot. It is due to transmetalation of Pd by an excess of base after removal of leftover Ag on consuming stoichiometric amounts of iodoarene.

Remarkably, this strategy is not only limited to the formation of C–C bonds, but also carbon–heteroatom bond formation can be achieved. Goossen and co-workers synthesized aryl ethers (**8a–m**) from benzoates with a concomitant protodecarboxylation process (Scheme 9).[60] They developed a method for copper and silver catalyzed regiospecific *ortho*-alkoxylation of aromatic carboxylates using trialkyl borates as an alkoxide source so as to

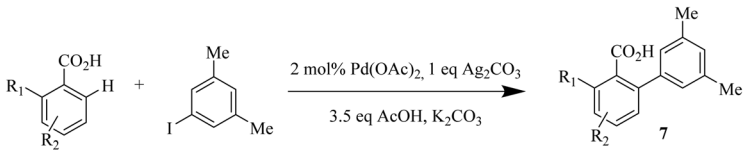



Scheme 6 *meta*-Selective direct arylation using iodoarenes.



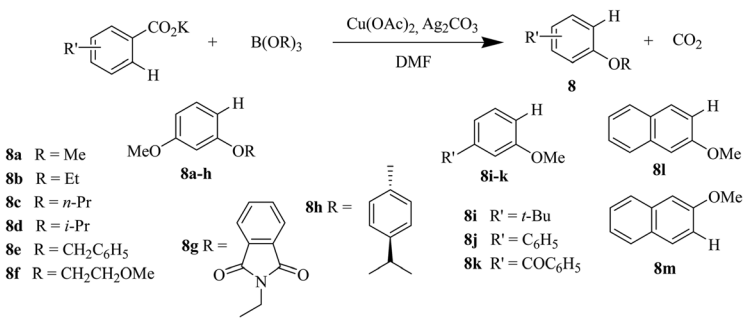

**6a** $R_1 = R_2 = H$, Ar = 4-(*t*-Bu)-$C_6H_4$
**6b** $R_1 = R_2 = H$, Ar = 4-MeO-$C_6H_4$
**6c** $R_1 = R_2 = H$, Ar = 4-Cl-$C_6H_4$
**6d** $R_1 = R_2 = H$, Ar = 2-naphthyl
**6e** $R_1$ = Me, $R_2 = H$, Ar = Ph
**6f** $R_1$ = OMe, $R_2 = H$, Ar = Ph
**6g** $R_1$ = Cl, $R_2 = H$, Ar = Ph
**6h** $R_1$ = Br, $R_2 = H$, Ar = Ph
**6i** $R_1$ = Ph, $R_2 = H$, Ar = Ph
**6j** $R_1$ = Ac, $R_2 = H$, Ar = Ph
**6k** $R_1 = CF_3$, $R_2 = H$, Ar = Ph
**6l** $R_1 = H$, $R_2$ = OMe, Ar = Ph
**6m** $R_1 = H$, $R_2$ = Cl, Ar = Ph
**6n** $R_1 = H$, $R_2$ = F, Ar = Ph

Scheme 7 Rhodium catalyzed olefination of benzoic acids.




**7a** $R_1 = R_2$ = Cl
**7b** $R_1$ = Cl, $R_2$ = F
**7c** $R_1$ = Cl, $R_2 = H$
**7d** $R_1$ = F, $R_2 = H$
**7e** $R_1 = R_2$ = F
**7f** $R_1 = R_2$ = OMe
**7g** $R_1$ = Cl, $R_2$ = OMe
**7h** $R_1 = CF_3$, $R_2 = H$
**7i** $R_1$ = OMe, $R_2 = H$
**7j** $R_1 = R_2 = H$

Scheme 8 Synthesis of 2-aryl-6-substituted benzoic acids by switching off the decarboxylation process.



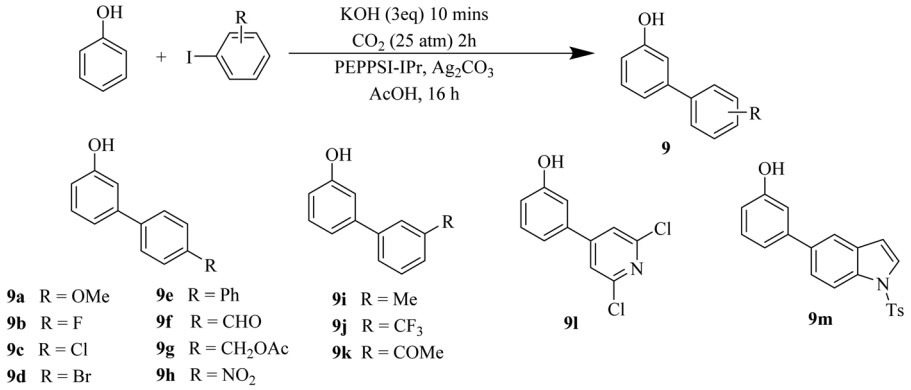

Scheme 9 Synthesis of aryl ethers from benzoates with the protodecarboxylation process.

provide access to a synthetically important class of substrates. Aromatic carboxylates possessing both electron-withdrawing and electron-donating groups were smoothly converted, and a wide range of substituents, including keto, cyano, nitro, sulfonyl, N-heterocyclic, and even bromo substituents, were well tolerable and produced good yields of compounds. As it was evident from previous literature that both copper and silver salts assist in the protodecarboxyation process, it was attempted to carry out the reaction in the absence of silver salt by using an extra equivalent of Cu salt, hypothesizing that it could serve in both alkoxylation and decarboxylation, but it didn't work and it was observed that the reaction cannot occur when a silver salt is used as a co-catalyst. Thus, its use was decisive as it promotes decarboxylation more efficiently in this reaction as compared to the Cu salt.

In 2014, Larrosa carried out both experimental and computational studies to understand the mechanism of silver catalyzed decarboxylation of *ortho*-substituted benzoic acids. He realized that by virtue of combined steric and electronic effects, the activation energy barrier is much lower in the case of *ortho*-substituents as compared to *meta*- and *para*-substituents.

It is well established that the electron releasing nature of hydroxyl groups directs the substitution at the *ortho*- and *para*-positions but it was first realized by Larrosa in 2014 in another publication that *meta* substituted phenols (**9a–m**) could be synthesized by adopting the traceless chelation strategy of carboxyl directing groups (Scheme 10).[61] He developed a new strategy for the synthesis of *meta*-substituted phenols and named it the traceless directing group relay strategy. In this strategy, carbon dioxide binds transiently to the *ortho*-position of the hydroxyl group, thereby facilitating *meta*-arylation to the hydroxyl group of phenol with iodoarenes using Pd as a catalyst and silver salt as an additive. This strategy helped in achieving the desired transformation, leaving behind no traces of carbon dioxide, with high regioselectivity and tolerance of a wide



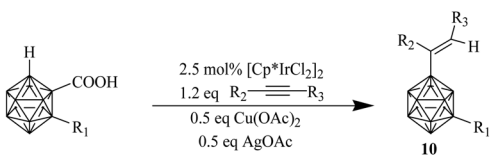

Scheme 10 Synthesis of *meta*-substituted phenols.

variety of functional group substituents on both the coupling partners.

These remarkable applications of carboxylic acid as a traceless directing group have motivated chemists to practice some unprecedented transformations. Thus, in this regard, a unique study of B–H activation was carried out by Quan and Xie in 2014. They have achieved iridium catalyzed B–H activation using carboxylic acid as a traceless directing group (Scheme 11),[62] leading to the formation of a series of 4-B-alkenylated-*o*-carboranes (**10a**–**s**) in high yields with excellent regioselectivity. This selective synthesis of B(4)-alkenylated-*o*-carboranes in a one pot fashion served as a blueprint for catalytic functionalization of carboranes at the 4,5,7,11-boron positions. According to the mechanism proposed by them, the reaction proceeds through an acid base reaction of the substrate with Ir(III), followed by electrophilic attack at the $B_4$ site, which subsequently undergoes alkyne insertion to form an iridacycle intermediate, which subsequently undergoes protodecarboxylation to form the desired product selectively and effectively (Scheme 12).

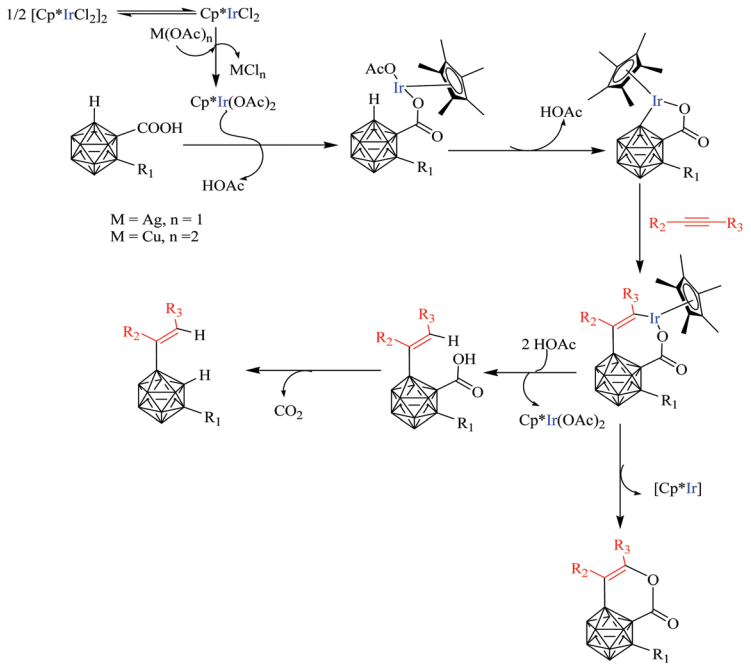
Maiti and his co-workers carried out the synthesis of 3-substituted benzofurans (**11a**–**m**) by intermolecular annulation of phenols with cinnamic acids using carboxylic acid as a directing group.[63] The reaction tolerated a variety of functional groups well on both the substrates such as chloro, bromo, fluoro, nitro, cyano, alkyl, alkoxy *etc.* It was observed that cinnamic acids offered orthogonal selectivity as compared to phenols. This approach occurred through a reaction sequence of C–C bond formation followed by tandem decarboxylation and cyclization. In 2015, this work was further extended by generalizing the acidic substrate (cinnamic acid) to α, β-unsaturated carboxylic acids to synthesize the corresponding benzofurans (**11n**–**q**) under the same reaction conditions as used in the previous report. The reaction has found wide applications in the synthesis of biologically active benzofuran alkaloid motifs (Scheme 13).[64]

In 2015, the Su and You groups developed independently a rhodium catalyzed method for oxidative $C_2$ arylation of a wide variety of heteroarenes such as thiophenes, furans, *N*-protected indoles *etc.* with aromatic carboxylic acids (**12a**–**k**) by using a silver salt as an additive (Scheme 14).[65,66] The reaction was initially tried with a Pd-catalyst and silver salt but it delivered the dimerized heteroarene product instead of giving the assumed target, but it was then replaced with a rhodium catalyst. This method has good functional group tolerance when different thiophene derivatives were used. With slight modifications in the reaction conditions, a variety of carboxylic acids with different substituents could be used. Due to the diverse occurrence of the thiophene moiety in a variety of natural and biologically active scaffolds, Su and his co-workers illustrated the application of his method by applying it for synthesis of an intermediate for a 17-β-hydroxysteroid dehydrogenase type-I inhibitor. They achieved its gram scale synthesis in one step by using easily accessible inexpensive starting materials, which served as the best step and atom economic alternative to its conventional synthesis by a Suzuki reaction. It was postulated by

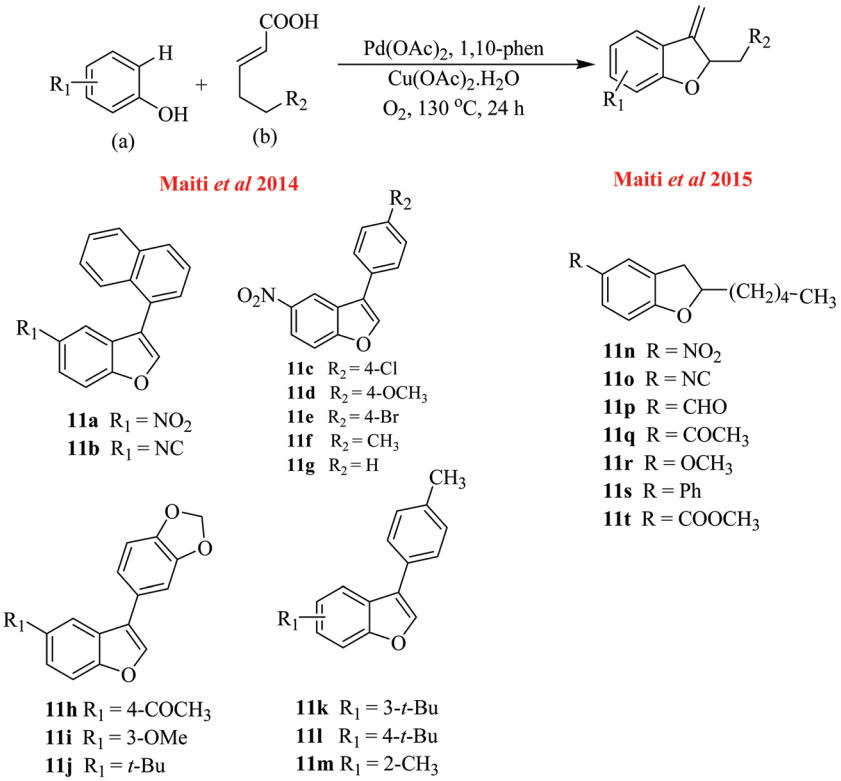



**10a** $R_1$ = H $R_2$ = $R_3$ = $C_6H_5$
**10b** $R_1$ = H $R_2$ = $R_3$ = 4-Me-$C_6H_4$
**10c** $R_1$ = H $R_2$ = $R_3$ = 3-Me-$C_6H_4$
**10d** $R_1$ = H $R_2$ = $R_3$ = 2-Me-$C_6H_4$
**10e** $R_1$ = H $R_2$ = $R_3$ = 4-*t*Bu-$C_6H_4$
**10f** $R_1$ = H $R_2$ = $R_3$ = 4-*i*Pr-$C_6H_4$
**10g** $R_1$ = H $R_2$ = $R_3$ = 4-Cl-$C_6H_4$
**10h** $R_1$ = H $R_2$ = $R_3$ = 3-Cl-$C_6H_4$
**10j** $R_1$ = H $R_2$ = $R_3$ = 4-F-$C_6H_4$
**10k** $R_1$ = H $R_2$ = $R_3$ = 4-Br-$C_6H_4$
**10l** $R_1$ = H $R_2$ = $R_3$ = 4-MeO-$C_6H_4$
**10m** $R_1$ = H $R_2$ = $R_3$ = 4-MeS-$C_6H_4$
**10n** $R_1$ = H $R_2$ = $R_3$ = 4$MeO_2C$
**10o** $R_1$ = H $R_2$ = $R_3$ = $CH_2C_6H_4$
**10p** $R_1$ = H $R_2$ = $R_3$ = 4-$MeO_2C$-$C_6H_4$
**10q** $R_1$ = H $R_2$ = $R_3$ = thiophenyl
**10r** $R_1$ = Me $R_2$ = $R_3$ = $C_6H_5$
**10s** $R_1$ = $C_6H_5CH_2$ $R_2$ = $R_3$ = $C_6H_5$

Scheme 11 Synthesis of a series of B-(4)-alkenylated-*o*-carboranes.



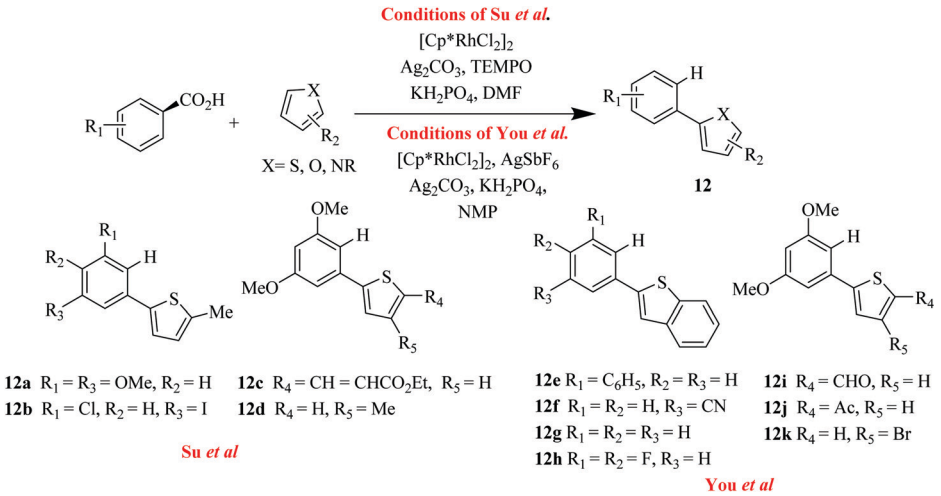

Scheme 12 Mechanism for Ir-catalyzed B–H activation.



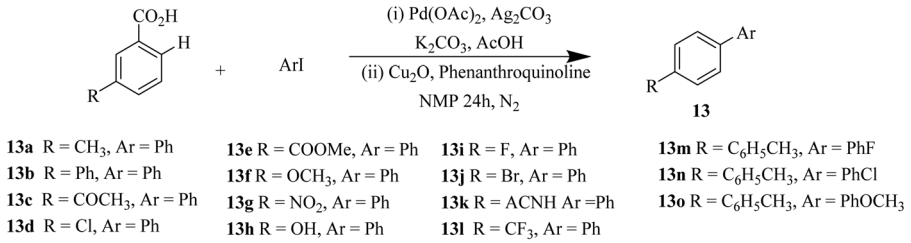

Scheme 13 Intermolecular annulation of phenols with carboxylic acids.

You and co-workers that the detailed mechanism of the reaction is not clear, but a plausible mechanism has been proposed by them. The catalyst undergoes carboxylation through ligand exchange to form active Rh(III) carboxylate species followed by electrophilic C–H activation at the *ortho*-position to form a rhodacycle intermediate followed by reaction with heteroarenes. This was subsequently followed by reductive elimination and protodecarboxylation to give the heteroarylated product.



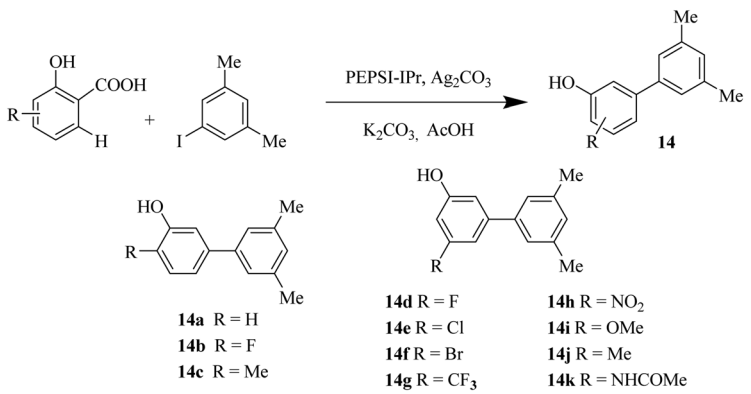

Scheme 14 Rhodium catalyzed oxidative $C_2$ arylation of heteroarenes.



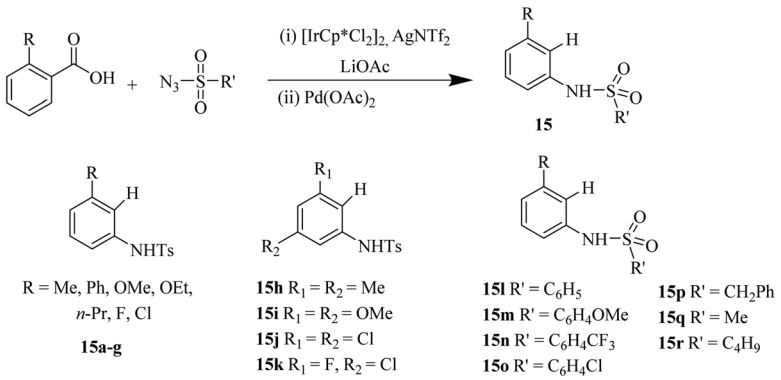

Scheme 15 Synthesis of *para*-substituted arenes.

A large number of *ortho*-arylation methods have been developed with a few *meta*-arylations of benzoic acids, while *para*-substitutions remained uninvestigated. Thus, Pan *et al.* in 2015 developed a versatile approach for the synthesis of *para*-substituted arenes using a multi-catalytic approach (Scheme 15).[67] The reaction proceeded through prior Pd-catalyzed selective functionalization of substituted carboxylic acids at the *ortho*-position followed by copper catalyzed protodecarboxylation to give *para*-substituted arenes (**13a–o**). Upon slight modifications in the reaction conditions, they revealed that besides the phenyl group, two other substituents *i.e.* hydroxyl and benzoyl groups could effect hydroxylation and carbonylation, which were followed by subsequent copper catalyzed protodecarboxylation.

After that, Larrosa and his co-workers investigated the synthesis of *meta*-arylated phenols (**14a–k**) with tandem arylation/decarboxylation from a variety of easily accessible salicylic acids (Scheme 16).[68] The reaction conditions were optimized, and it was observed that PEPSI-IPr was suited as an excellent catalyst to facilitate the desired transformation. It was also revealed that there is poor tolerance of substitution at the C5-position of salicylic acid, which is due to steric hindrance. Thus, methyl and chloro at the C5-position of salicylic acid do




Scheme 16 Synthesis of *meta*-arylated phenols *via* tandem arylation/decarboxylation.

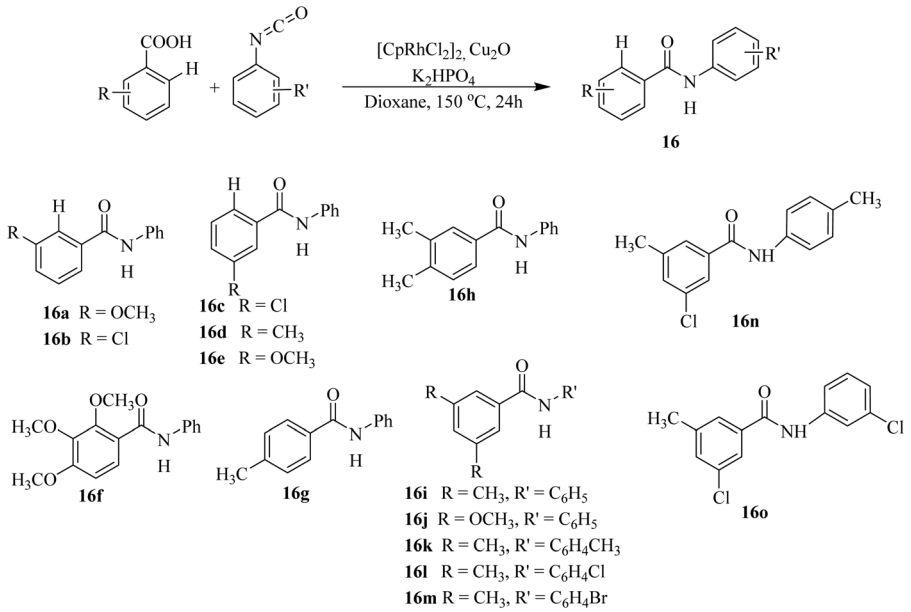



Scheme 17 Iridium catalyzed mild amidation of benzoic acids with sulfonylazides.

not react at all. However, the smaller fluoro atom at the same position afforded the product in moderate yield. To generalize this method of synthesis for industrial purposes, the reaction yield was examined by replacing the expensive silver salt with economically cheap and easily accessible $NMe_4Cl$, which turned out to be a suitable alternate to effect the transformation, delivering the desired products in good yields.

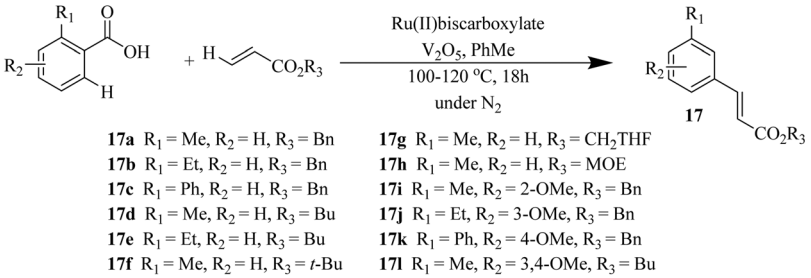
Chang and his co-workers developed a method for one pot decarboxylative amidation of benzoic acids (Scheme 17).[69] It was reported that iridium catalyzed mild amidation of benzoic acids with sulfonylazides delivered *ortho*-amidated benzoic acids (**15a–r**), which on subsequent palladium catalyzed protodecarboxylation afforded *meta*-substituted arenes with high efficiency and functional group compatibility. Although these *meta*-substituted products would be obtained by Hartwig's method of tandem borylation and amidation, this method paved a path to think about synthesis of *para*-amidated compounds by C–H activation on using 3-substituted benzoic acids instead of 2-substituted. It was seen that this theoretical prediction turned out to be true when the method was tried. They succeeded in applying the same conditions for synthesis of *para*-amidated products which were not accessible by Hartwig's approach.

One more analogous amidation was reported in the same year by Shi *et al.* (Scheme 18).[70] They accessed the synthesis of *N*-aryl benzamides (**16a–o**) through rhodium catalyzed selective amidation of substituted benzoic acids with isocyanates using a catalytic amount of $Cu_2O$ for subsequent protodecarboxylation. They realized that although the desired product could be obtained even in the absence of $Cu_2O$, the yield was too low. This observation revealed the fact that rhodium has the ability to promote protodecarboxylation. So, they extended their work by examining different metals which could efficiently catalyze both steps, eliminating the need for $Cu_2O$. Finally, they succeeded in their attempts and it was reported that replacing rhodium with ruthenium eliminates the use of $Cu_2O$ for protodecarboxylation. During this period, ruthenium was also proven to have some extraordinary capacity to promote protodecarboxylation after an *ortho* C–H functionalization reaction in one pot.




Scheme 18 Synthesis of *N*-aryl benzamides through rhodium catalyzed selective amidation.



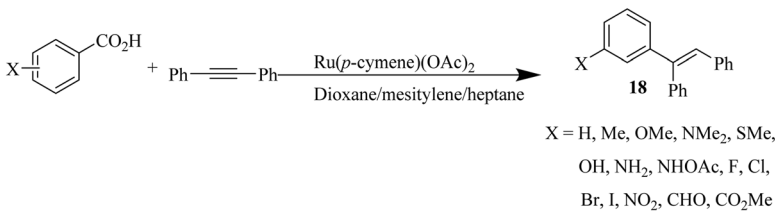

Scheme 19 Synthesis of *meta*-substituted arenes by a ruthenium(II) biscarboxylate complex.

It was further demonstrated by independent work of several teams such as Ackermann, Goossen, Larrosa and Zhao. Ackermann carried out unprecedented ruthenium catalyzed oxidative C–H functionalization through a decarboxylative mechanism, which furnished *meta*-substituted arenes (**17a–l**) with high chemo-, positional-, and regio-selectivity without delivering any *ortho*-substituted products. The reaction was catalyzed by a user-friendly and highly versatile ruthenium(II) biscarboxylate complex which showed ample substrate scope. Thus, this study was further extended to enable its viability for alkenylation in another publication by his group in the same year (Scheme 19).[71]

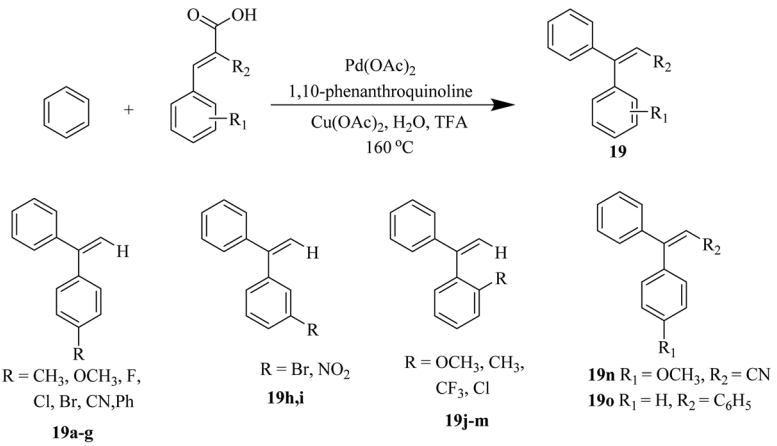
Similarly, Zhao and co-workers reported ruthenium catalyzed hydroarylations of alkynes to furnish alkenylarene products (**18**) with versatile regioselectivity. Moreover, mild reaction conditions (low temperature and neutral redox conditions) are well suited for various aromatic substituents present at *ortho*-, *meta*-, and *para*-positions (Scheme 20).[72] Meanwhile, Larrosa and Simonetti carried out coupling of alkynes and a benzoate substrate furnishing a *meta*-substituted alkenylated product.[73] A similar approach was used by Huang and Weix in which arylation of carboxylic acids with diverse aryl halides (iodide, bromide, and triflate; aryl and heteroaryl) was carried out.[74]

However, in 2016, Maiti and his co-workers developed a novel strategy for synthetically vital branched olefinated products of benzene (**19a–o**). They reported palladium catalyzed highly selective olefination of a completely unbiased benzene ring with branched olefins facilitated by a traceless carboxyl directed C–H activation based protocol (Scheme 21).[75] The reaction proceeded through palladium catalyzed selective insertion of olefins followed by copper catalyzed protodecarboxylation. The reaction exhibited high functional group tolerance and further the olefinated products were subjected to late stage functionalization to demonstrate the applicative potential of the newly developed protocol.

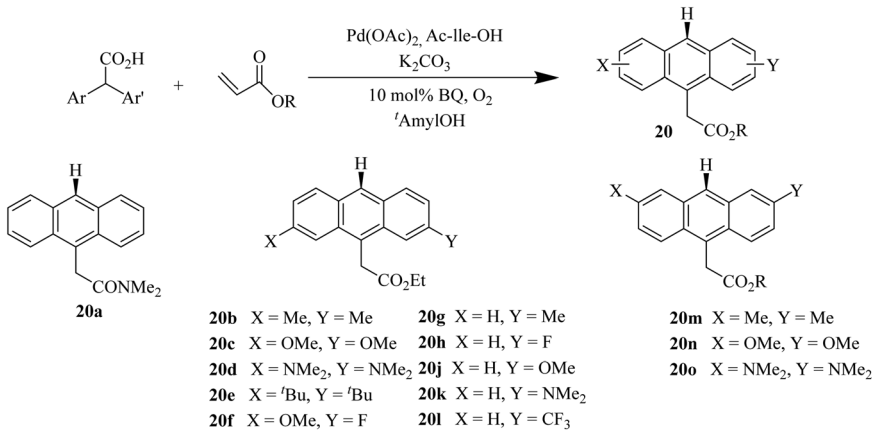
Hong and co-workers synthesized pharmacologically vital heteroacene derivatives through a simple Pd(II)-catalyzed tandem conversion involving carboxyl-directed secondary C–H activation




Scheme 20 Ruthenium catalysed hydroarylations of alkynes to furnish alkenylarene.



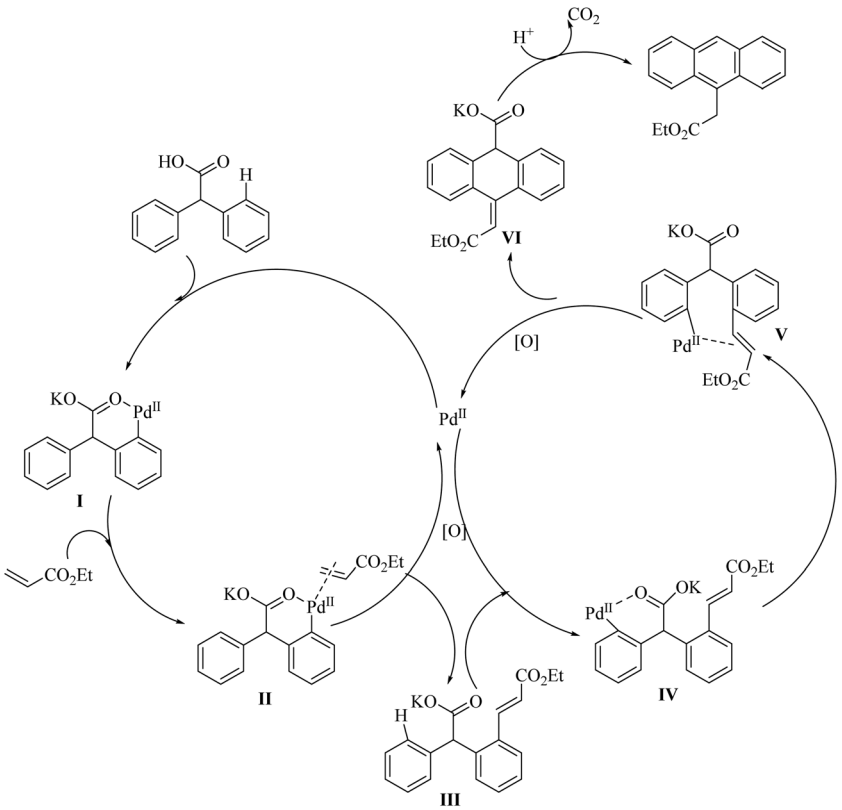

Scheme 21 Palladium catalyzed strategy for the development of branched olefinated products of benzene.




Scheme 22 Synthesis of anthracene derivatives.

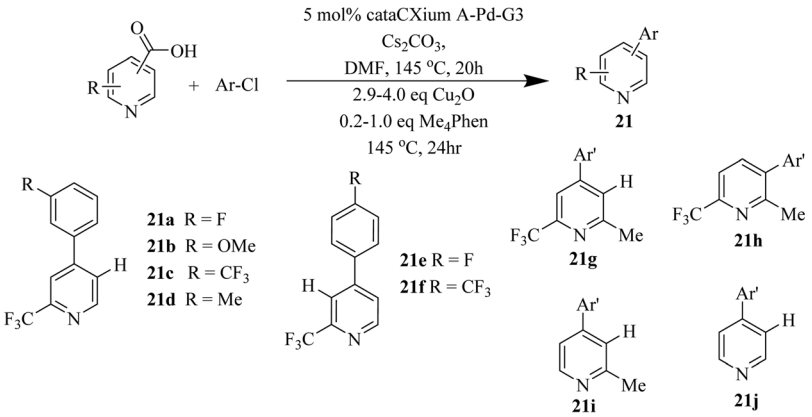
of diaryl carboxylic acids with acrylates followed by decarboxylative intramolecular aromatization (through cyclisation) involving C–C bond formation, affording the desired anthracene products (**20a–o**). This served as a step economical novel approach for the synthesis of heterocene derivatives (Scheme 22).[76] The plausible mechanism (Scheme 23) involves the direction of a carboxylic group for C–H activation in one of the phenyl rings in diaryl carboxylic acids, forming a palladacycle intermediate, which was followed by alkene coordination to give an olefinated intermediate. Then, this olefinated intermediate undergoes carboxyl directed C–H cleavage followed by roll-over and intramolecular cyclization to form a cyclized intermediate, which upon decarboxylation yields the desired anthracene product. Molecular oxygen serves the purpose of regeneration of Pd(II) species, thereby completing the catalytic cycle.

A competing experiment of pyridine-3-carboxylic acid showed that carboxylic acid has the ability to overrule the DG ability of Lewis base $sp^2$-nitrogen of pyridine. The method allowed Pd-catalyzed regioselective C-3/C-4 arylation of pyridine-3-carboxylic acid and its derivatives followed by copper catalyzed decarboxylation, delivering biologically active pyridine biaryls (**21a–j**) using low cost and easily accessible chloro- and bromo-arenes as coupling partners




Scheme 23 Mechanism for the synthesis of heterocene derivatives.

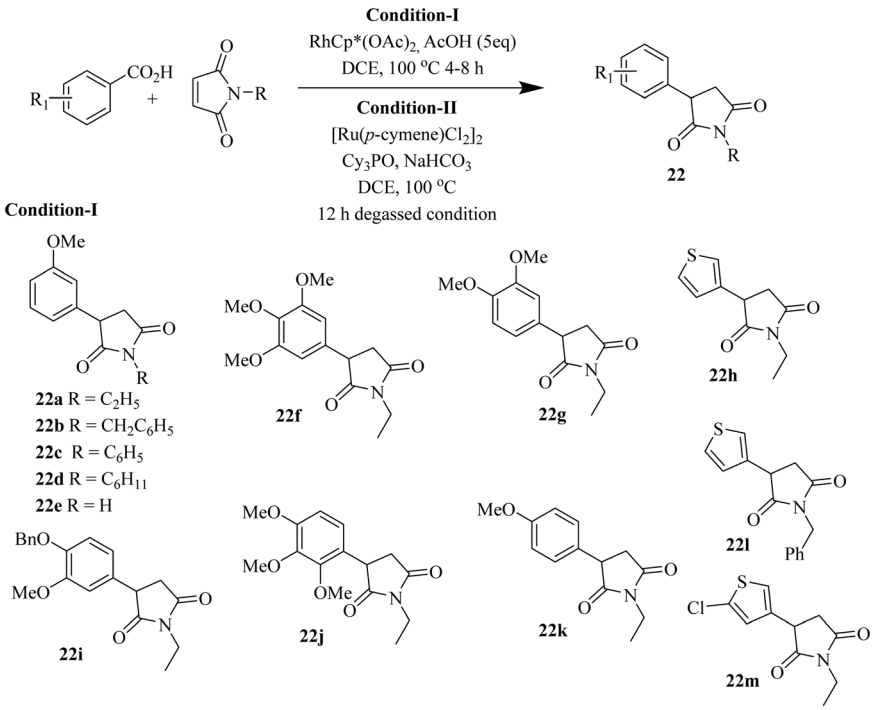



Scheme 24 Pd-Catalyzed regioselective C-3/C-4 arylation of pyridine-3-carboxylic acid.

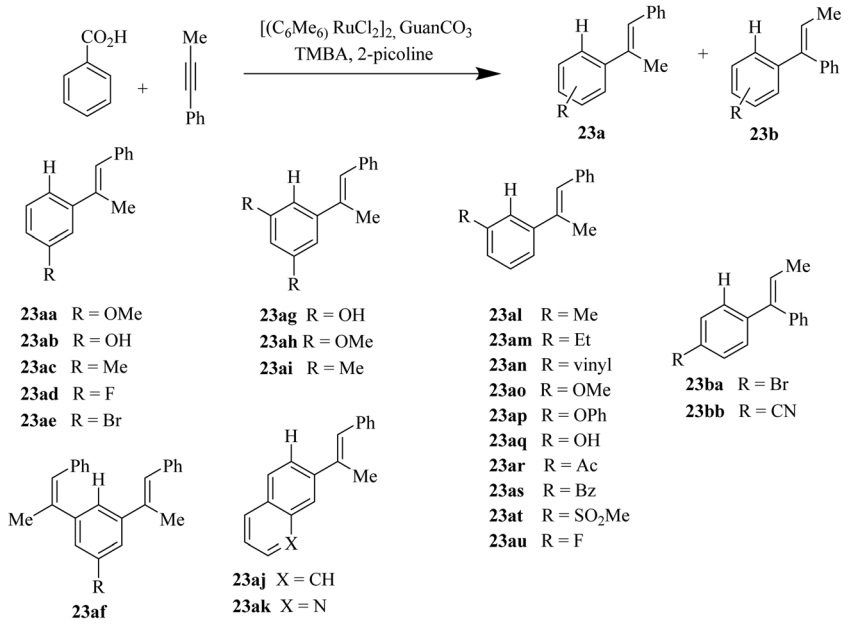
(Scheme 24).[77] The reaction has a wide range of substrate scope with electron-donating and -withdrawing groups as well as aryl moieties. This was the first strategy for traceless directing group assisted synthesis of C-4 arylated pyridines.

In 2017, Prabhu and co-workers carried out conjugate addition of maleimides to benzoic acids *via* Rh(III)-catalyzed C–H activation using carboxylic acid as a traceless group to furnish a series of 3-aryl succinimides (**22a**–**m**). The reaction exhibited a wide substrate scope where different substituted succinimides were used (Scheme 25).[78] With slight modifications in the reaction conditions, other heterocyclic carboxylic acids such as thiophene and 5-chlorothiophene also resulted in the desired products in good yields, while furan, pyrrole and indole carboxylic acids afforded low yields of products. The authors further extended the substrate scope of acids to acrylic acids to furnish 3-vinyl succinimides. Soon after this, Baidya and co-workers carried out the same transformation with maleimide to substituted aryl succinimides but they used a ruthenium catalyst instead of a Rh catalyst.[79] Ackermann and co-workers have carried out a computational study of a somewhat similar coupling of maleimides to acids.[80]

In another approach, Goossen and co-workers in 2017 used an inexpensive and easy-to-handle catalyst $[(C_6Me_6)RuCl_2]_2$ for doubly regioselective C–H hydroarylation of unsymmetrical alkynes (Scheme 26).[81] The reaction proceeded through concerted regioselective alkyne addition and decarboxylation to yield exclusively the monovinylated product (**23**) with high regioselectivity. Meanwhile, in the same year, Hong and co-workers carried out computational studies to explain the mechanism and chemo- and regio-selectivities of Ru(II)-catalyzed decarboxylative C–H alkenylation of aryl carboxylic




Scheme 25 Conjugate addition of maleimides to benzoic acids.

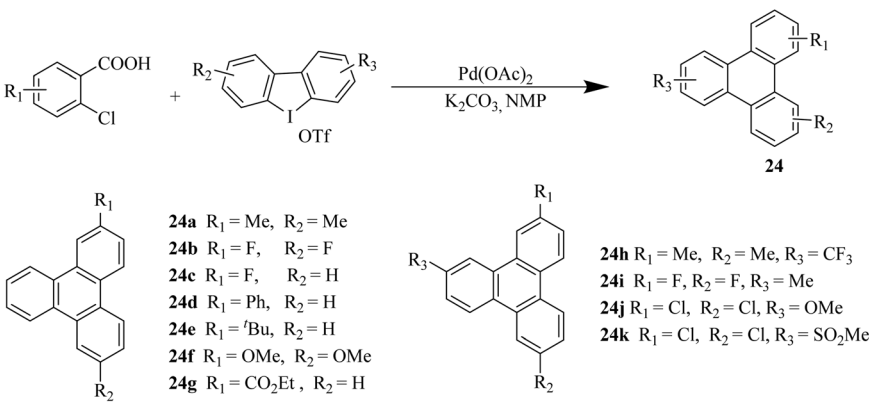



Scheme 26 Regioselective alkyne addition to yield exclusively monovinylated products.

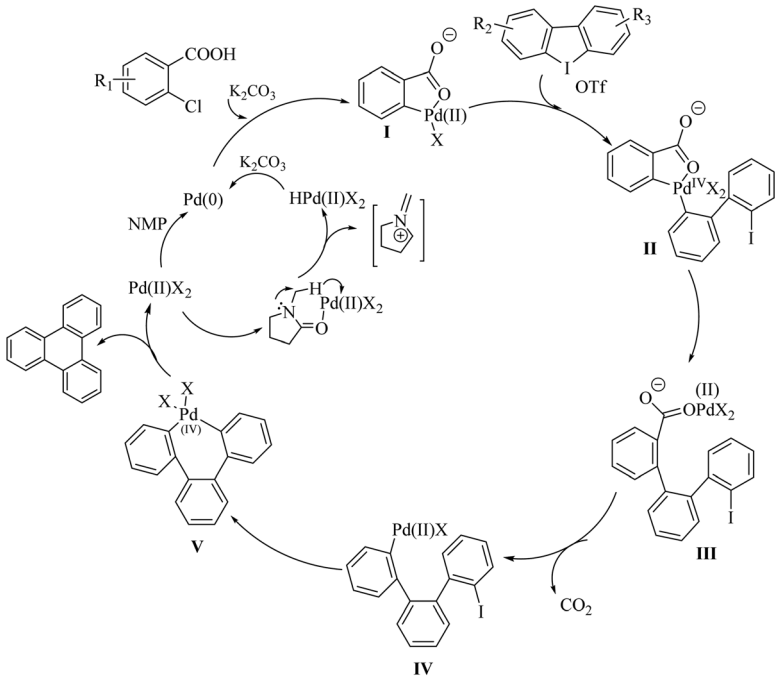
acids with alkynes by using Density Functional Theory (DFT) calculations.[82] The reaction begins with carboxylic group directed C–H activation at the *ortho*-position, leading to the formation of an *ortho*-ruthenated complex, which further undergoes alkene insertion to form a seven membered ruthenacycle intermediate that forms the desired product after decarboxylation and protodemetalation.

In 2018, Zhang and co-workers used this traceless strategy to develop a novel and efficient ligand free one pot procedure for the valuable synthesis of triphenylenes (**24a–k**) from easily accessible *ortho*-halo benzoic acids and cyclic diaryliodonium salts (Scheme 27).[83] It involved a Pd-catalyzed cascade reaction which afforded tandem *ortho*-arylation of the substrate and intramolecular decarboxylative annulations. This was the first report demonstrating the reaction of cyclic diaryliodonium salts with aryl halides through traceless direction of the carboxylic group where diaryliodonium salts aided in π-extension. With the means of previous literature reports and control experiments carried out by the research group, they proposed a mechanism in which carboxyl directed arylation at the *ortho*-position has been done followed by intramolecular decarboxylative arylation/cyclisation. Initially, *ortho*-chlorobenzoic acid gave rise to a five-membered Pd(II) complex, which gave rise to a Pd(IV) complex by attacking the cyclic diaryliodonium salt. This thereafter gives rise to another seven membered Pd(IV) complex after reductive elimination, decarboxylation and cyclization. This seven membered complex intermediate further undergoes reductive elimination to form the desired triphenylene products (Scheme 28).

There were several methods available for selective *ortho*-arylation of fluoroarenes but it was in 2018 that Larrosa and his co-workers carried out *meta* C–H arylation of fluoroarenes selectively by employing carbon dioxide as a traceless directing group. They carried out arylation of various substituted fluoroarenes where carbon dioxide binds transiently and directs the process under Pd-catalyzed conditions. The reaction is compatible with a variety of substituents (nitro, methyl, ester and



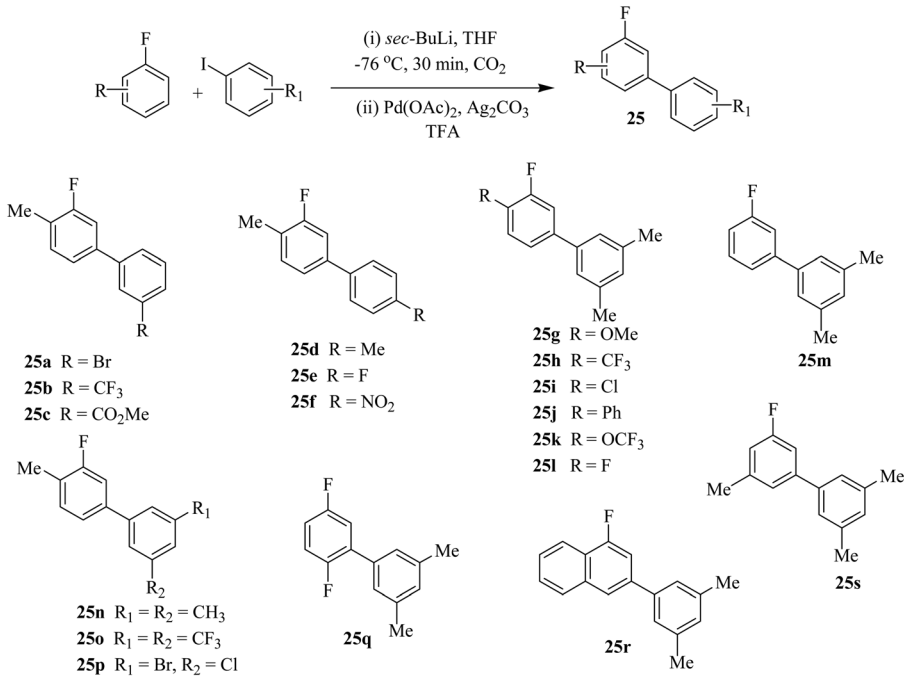

Scheme 27 Synthesis of triphenylene derivatives.



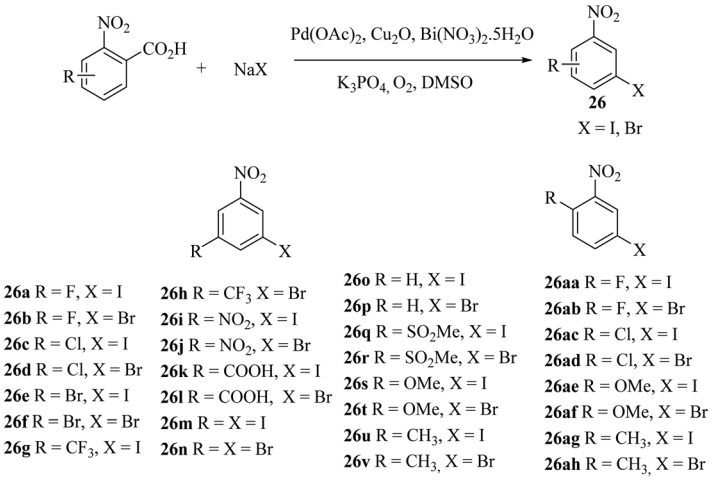

Scheme 28 Mechanism for the synthesis of triphenylenes.

trifluoromethyl) with respect to both fluoroarenes and aryl iodide substrates. The reaction occurred through a protocol involving lithiation and carboxylation followed by tandem arylation and decarboxylation. Since the reaction enabled the synthesis of fluoro(biaryl)hetero moieties (**25a–s**), therefore it could be applied to the synthesis of top selling pharmaceutical moieties such as Rosuvastatin and Atorvastatin (Scheme 29).[84]

There have been numerous reports available for arylation, alkylation, alkynylation and annulation reactions directed by traceless carboxylic acid, but in 2019 Cai and co-workers were the first to demonstrate *ortho*-halogenation of substituted benzoic acids. They developed a novel method to carry out the carboxyl directed Pd-catalyzed regioselective halogenation of nitrobenzoic acids to afford *m*-nitro halobenzenes (**26a–v**, **26aa–ah**) using




Scheme 29 Selective *ortho* arylation of fluoroarenes.



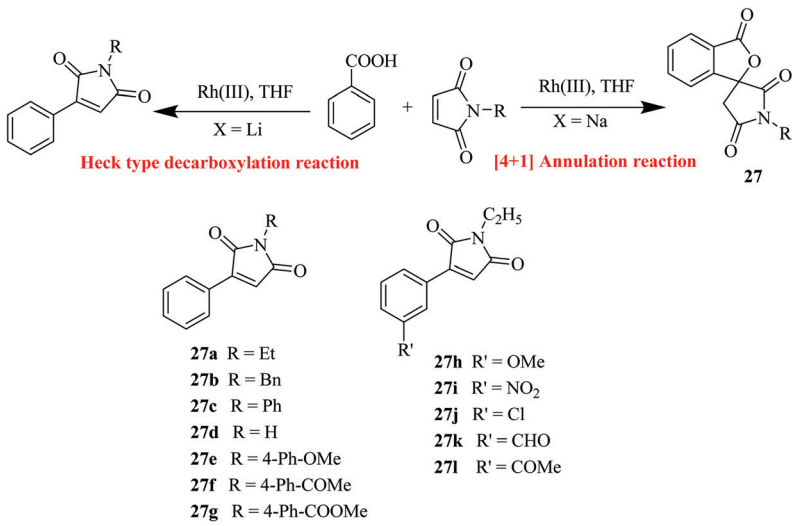

Scheme 30 Pd-Catalyzed regioselective halogenation of nitrobenzoic acids.

sodium halides (as a halogen source) under aerobic conditions (Scheme 30).[85] Mechanistic studies revealed that the Bi salt played a vital role for the transformation to occur efficiently and the product formed was further diversified using different substitutions to ensure the applicability of the process.

Very recently, Prabhu and co-workers extended his earlier study of activation of maleimides (Scheme 31).[86] They reported the reaction of carboxylic acid with maleimide whereby merely changing the solvent could help in switching the two reactions (*viz.* Heck type and [4+1] annulation reactions) to afford two switchable products. The solvent played a vital role in controlling this switching, where aprotic solvent THF favored the decarboxylative Heck type reaction, while a protic solvent followed the [4+1] annulation reaction. The reaction was also highly dependent on the nature of the solvent for its desired selectivity and tolerated functional groups well. The Heck reaction proceeded through a decarboxylation process where the carboxyl group served as a traceless directing group, resulting in the formation of arylated maleimides (**27a–l**).

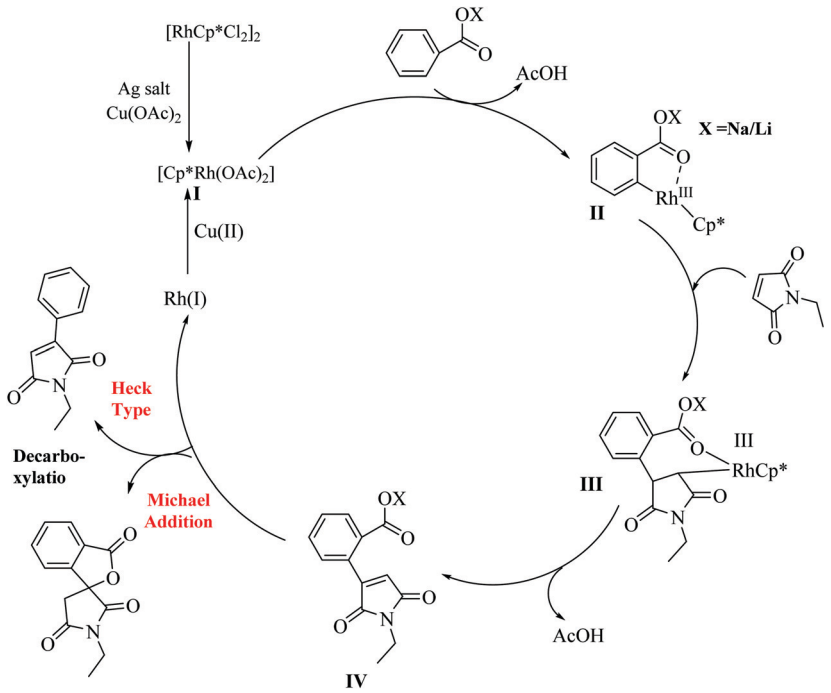
According to mechanistic studies conducted by Prabhu's group, it was revealed that the reaction follows ligand exchange of the catalyst with cupric and silver salts to give the active form of catalyst **I**. Following this, an aromatic acid undergoes metallization with **I** to give five-membered rhodacycle intermediate **II**, which endures coordination and insertion of maleimide to form a bicyclic intermediate **III** rigid geometry. Intermediate **III** undergoes elimination *via* an $E_2$ mechanism giving intermediate **IV**. This intermediate **IV** could either undergo a Heck type decarboxylation reaction or [4+1] annulation reaction depending upon the solvent in which the reaction is carried out. In an aprotic solvent such as THF it prefers to undergo decarboxylation due to the almost negligible availability of protons. However, in the presence of protons (*i.e.* in a protic solvent such as TFE), benzoic acid salts convert to their corresponding acid, preventing the decarboxylation reaction (Scheme 32).

Generally, the most common approach used for *meta* olefination is through the aid of a large *meta* directing template,




Scheme 31 Switchable decarboxylative rhodium(III) catalyzed Heck type and [4+1] annulation reaction with maleimides.

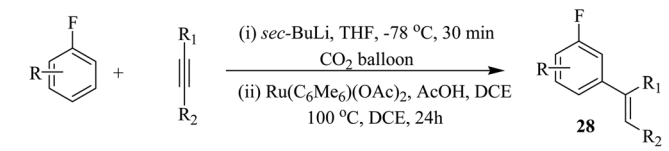
 




Scheme 32 Plausible mechanism for the switchable decarboxylative rhodium(III) catalyzed Heck type and [4+1] annulation reactions with maleimides.

which cannot be used in the case of fluoroarene substrates as they are unable to be derivatized. Thus, Larrosa and his co-workers extended their previous work of *meta*-functionalization of fluoroarenes in 2020 where they developed a novel method for *meta* selective olefination of fluoroarenes in which carbon dioxide binds transiently to the fluoroarene and departs from the functional moiety after directing the olefination selectively at the *meta* position and without the use of any template, enabling the synthesis of olefinated fluoroarenes (**28a–v**). The reaction gained extra attention due to elimination of the use of stoichiometric Ag salts which were earlier commonly used for carrying out selective olefination (Scheme 33).[87]

**2.1.2 Aldehyde as a traceless directing group.** The aldehyde group is one of the most diversely occurring functional groups due to its high prevalence in a wide spectrum of naturally and synthetically occurring organic products. But due to its weak affinity of coordination, high potential to get deformylated and facile ability to get oxidized under oxidizing conditions, it has been rarely employed to serve the purpose of a directing group in metal catalyzed C–H activation reactions.

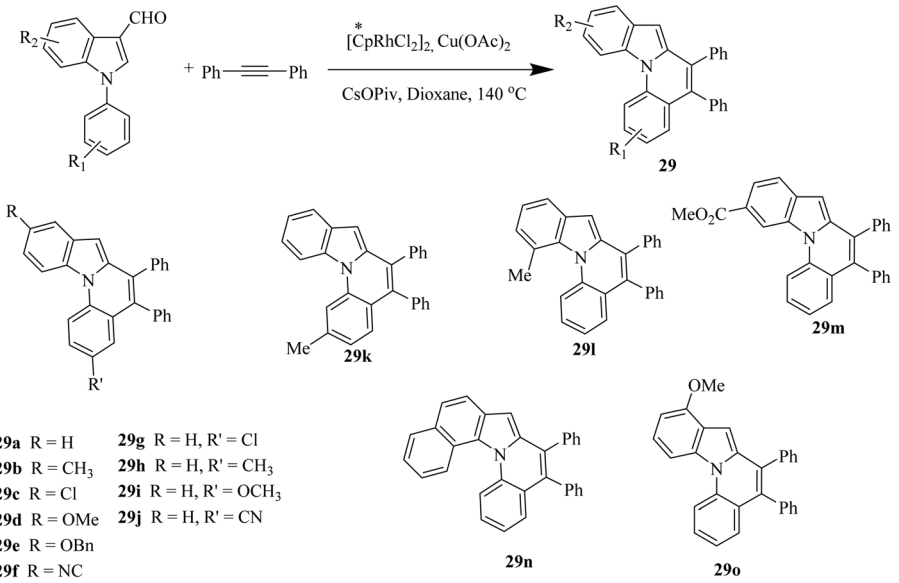



**28a** R = Me
**28b** R = H
**28c** R = OMe
**28d** R = Cl
**28e** R = $CF_3$
**28f** R = $OCF_3$
**28g** R = Ph

**28h** R = H
**28i** R = Me
**28j** R = Cl

**28k** $R_1 = R_2 = 4\text{-}C_6H_4\text{-}Me$
**28l** $R_1 = R_2 = n\text{-}Pr$
**28m** $R_1 = R_2 = 4\text{-}C_6H_4\text{-}Cl$
**28n** $R_1 = R_2 = 4\text{-}C_6H_4\text{-}CF_3$
**28o** $R_1 = R_2 = 4\text{-}C_6H_4\text{-}CN$
**28p** $R_1 = R_2 = 4\text{-}C_6H_4\text{-}Br$
**28q** $R_1 = R_2 = 4\text{-}C_6H_4\text{-}t\text{-}Bu$
**28r** $R_1 = R_2 = COOEt$
**28s** $R_1 = R_2 = 2\text{-thiophene}$
**28t** $R_1 = H$, $R_2 = Ph$
**28u** $R_1 = Me$, $R_2 = Ph$
**28v** $R_1 = CO_2Et$, $R_2 = Ph$

Scheme 33 *meta*-Olefination of fluoroarenes.

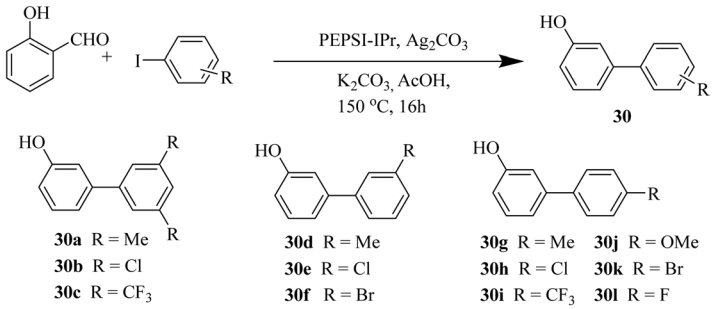



Scheme 34 Rh(III) catalyzed facile access to indolo[1,2-α]quinolines.

The hidden potential of the highly versatile aldehyde group to act as a traceless directing group was first realized by You and his co-workers in 2015. They provided Rh(III) catalyzed facile access to highly privileged polycyclic heteroatomic scaffold indolo[1,2-α]-quinolone (**29a–n**) (Scheme 34).[88] The protocol proceeded through Rh(III) catalyzed regioselective alkenylation of the indole core of 2-aryl-3-formylindoles followed by decarbonylation and annulation to furnish the desired cyclized product. The strategy was highly viable due to good tolerance of functional groups (alkoxy, chloro, fluoro, cyano and esters) which could be further employed for subsequent transformations. To illustrate the application of the novel protocol, a concise three step indoloquinoline based sensitizer was furnished. The latter was found to be highly appealing for the construction of optoelectronic materials.

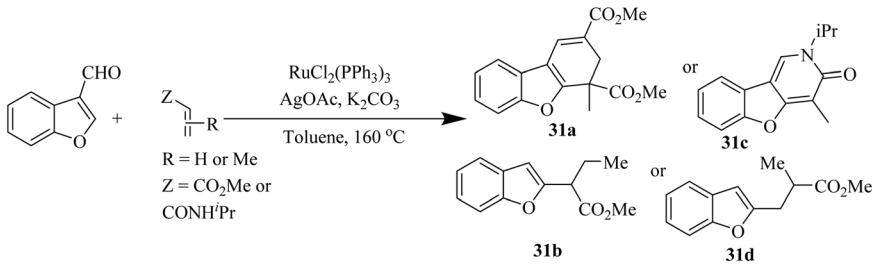
This remarkable ability of aldehydes was further exploited by the group of Larrosa in 2016. They reported PEPSI-IPr catalyzed site specific transformation of salicylaldehydes into *meta*-arylated phenols (**30a–l**) through tandem arylation of salicylaldehyde and deformylation occurring in a one pot fashion (Scheme 35).[89] While figuring out the mechanism of the catalytic methodology, they speculated that it could occur through either of three pathways: (i) arylation followed by decarbonylation, (ii) *ortho*-arylation followed by oxidation and protodecarboxylation and (iii) oxidation of salicylaldehyde followed by arylation and protodecarboxylation. To reveal which of these actually operates during the transformation, the crude reaction mixture was examined for analysis of the intermediates. It has been found that the reaction mixture does not contain any *ortho*-arylated salicylaldehyde intermediate, inferring that neither the (i) nor the (ii) pathway could occur as both follow the formation of an *ortho*-arylated salicylaldehyde intermediate. This leads to the inference that the transformation occurs through mechanistic pathway (iii). The substrate scope was examined using a variety of aryl iodides substituted at different positions with both electron-donating and electron-withdrawing groups. It was revealed that 3- and 4-substituted aldehydes were most suitable, giving excellent yields, while disubstituted aldehydes gave a moderate amount of products, whereas 5-substituted salicyladehydes were unreactive due to a lack of tolerance of substitutions at the *ortho*-positions.

Next, in 2019, Ramana and co-workers reported Ru-catalyzed alkylation of dibenzofurans with a variety of acrylates including unsubstituted, α-substituted and β-substituted acrylates (Scheme 36).[90] It has been observed that there was branched




Scheme 35 Site specific transformation of salicyladehydes into *meta*-arylated phenols.



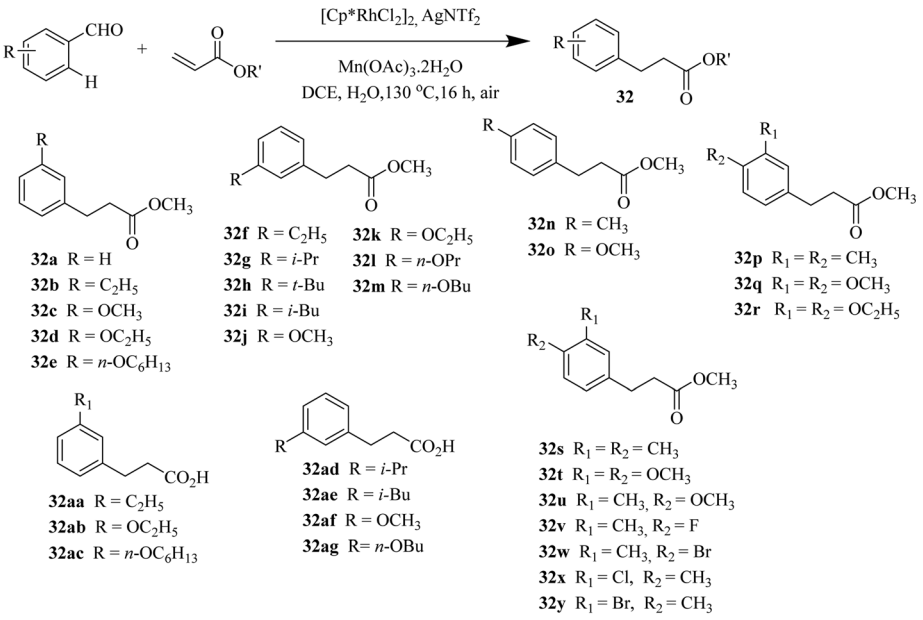

Scheme 36 Ru catalyzed alkylation of dibenzofurans with a variety of acrylates.

selectivity in unsubstituted and β-substituted acrylates and linear selectivity with α-substituted acrylates (**31**). The initially formed alkylated intermediate reacted further according to the other substrates. The reaction with methyl acrylate proceeded *via* further cycloannulation with another molecule of methyl acrylate, while the reaction with both methacrylate and crotonate underwent deformylation. On the other hand, with *N*-monosubstituted acrylamides, intramolecular aldehyde amide condensation was observed, which was subsequently followed by pyridin-2-one ring annulations.

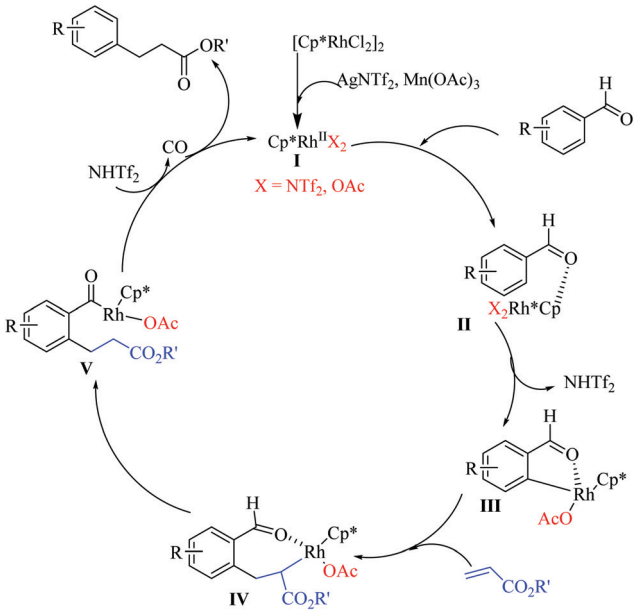
Very recently, in 2020, Rh(III)-catalyzed regioselective alkylation of aromatic aldehydes under aerobic atmospheric conditions was achieved by Shi and his co-workers (Scheme 37).[91] The reaction involved simple operation which occurred through *ortho*-alkylation of aromatic aldehydes with acrylates (**32a–y**) and acrylic acids (**32aa–ag**) followed by decarbonylation to furnish the alkylated derivatives. The reaction rate was affected by steric factors as the *ortho*-substituted substrates delivered the product in good yields as compared to electron rich *para*-substituted aldehydes. This may be due to the steric effect of *ortho*-substituents, which might favor coordination between the aldehyde and rhodium metal. It was also influenced by electronic effects as arenes containing electron-withdrawing groups such as halogens, $CF_3$, CN and $NO_2$ exhibited lower reactivity as compared to arenes containing electron rich groups. According to the preliminary mechanism studies, it was revealed that firstly $[Cp^*RhCl_2]_2$ undergoes ligand exchange with $Mn(OAc)_3$ and $AgNTf_2$ to generate active Rh(III) form **I**. This active form coordinates to carbonyl oxygen **II** followed by *ortho*-metalation to give 5-membered cyclic intermediate **III**. The acrylates undergo coordinative insertion to this complex intermediate followed by alkylation, decarbonylation and protodecarboxylation to give the final product (Scheme 38).

## 2.2 N–O bond based traceless directing groups

**2.2.1 *N*-Oxides.** *N*-Oxides have a functionally diverse polar N–O bond. This NO bond has been used for directing various metal catalyzed and metal free C–H functionalization reactions in synthetic chemistry. Moreover, this group has also served as an internal oxidant due to its remarkably exceptional Oxygen Atom Transfer (OAT) ability which was realized during its redox neutral coupling reaction of NO containing compounds with alkynes and alkenes. Taking a basic ideology from extensively used Ru catalyst [Cp*Ru(III)] where both OAT and C–H activation




Scheme 37 Rh(III) catalyzed regioselective alkylation of aromatic aldehydes.

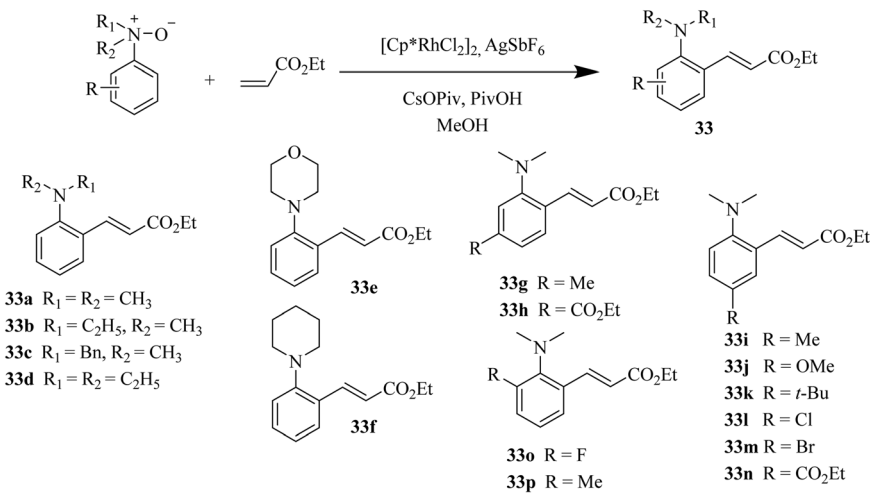



Scheme 38 Proposed mechanism for regioselective alkylation of aromatic aldehydes.

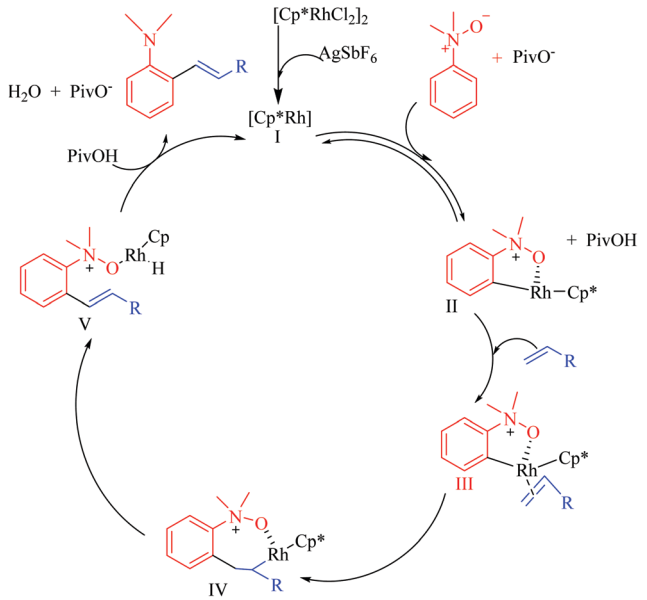
showed combined effects and operated simultaneously in a sequential manner, several researchers realized that these NO based directing groups also possess both the properties *i.e.* these could act as an internal oxidant as well as a directing group. They developed an elegant strategy of integration of both the properties in a C–H activation reaction. This fascinating concept of integration gives rise to a novel feature of a traceless nature with this directing group. These *N*-oxide based directing groups besides being traceless have an excellent property of readily coordinating to the metal centre. An additional advantage of using *N*-oxide as a directing group is that it also eliminates the need for any external oxidants and *N*-deprotection. Thus, various attempts were made to use *N*-oxide containing TDGs for directing C–H activation reactions.

One of the first attempts to use *N*-oxide as a traceless directing group was made by You and co-workers in 2013 (Scheme 39).[92] They have used tertiary aniline *N*-oxide to direct Rh catalyzed olefination to illustrate the novel strategy based on a group serving the purpose of an internal oxidant as well as directing the *ortho*-functionalization reaction. This methodology enabled the synthesis of *ortho*-substituted olefinated derivatives of tertiary amines (**33a–n**) overriding their conventional preference of *para*-substitution driven by combined effects of the electron releasing nature and steric hindrance of tertiary amines. Initially, an active Rh(III) species is generated from $[RhCp^*Cl_2]_2$ and $AgSbF_6$, which reacts with the *N*-oxide to form a cyclorhodium intermediate followed by an electrophilic C–H activation process and olefin coordination. Then, alkene undergoes migratory insertion, which is followed by β-hydride elimination and N–O bond cleavage to give the desired product (Scheme 40).

It is relatively easy to functionalize the C2 position of quinolines as compared to the C8 position. Thus, a new approach was developed where an *N*-oxide group was installed on the heterocyclic quinoline moiety to afford functionalization at the exceptional C8 position as the quinolines and their analogues are very common constituents in biologically active pharmacophores. Although installation of it requires an additional step, it is very easy to introduce an *N*-oxide group just by oxidation of the N-atom of quinolines by using peroxides. But there were some reactions in which it directed C8 functionalization reactions by subsequent removal of the oxide on its own after functionalization. One such kind of example is Rh(III) catalyzed highly selective olefination at the C8 position by Sharma and co-workers (Scheme 41).[93] Various substituted quinoline oxides with several labile functional moieties were olefinated with a wide variety of unactivated alkenes as well as styrenes and acrylates affording the corresponding C8-alkenylated quinoline products in moderate to good yields. The reaction occurs through the formation of a 5-membered cyclic intermediate synthesized through *N*-oxide directed bond




Scheme 39 Synthesis of *ortho*-substituted olefinated derivatives of tertiary amines.



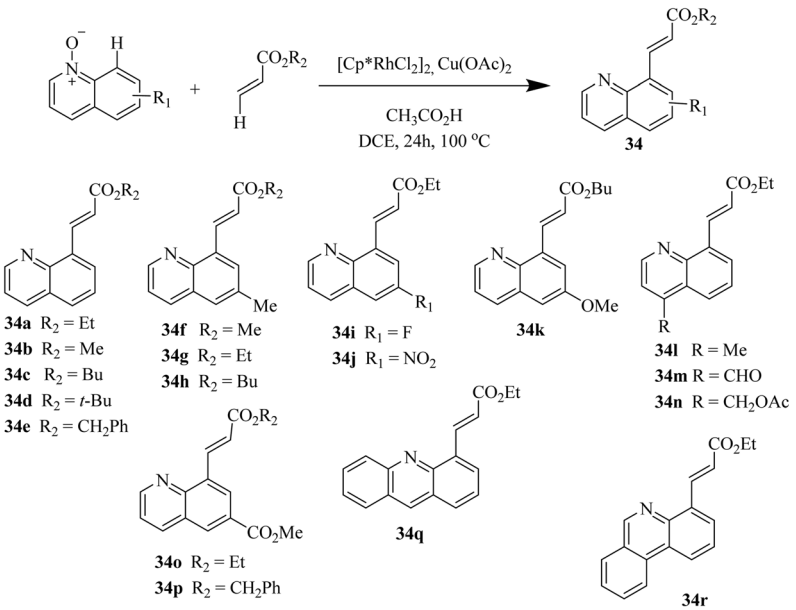

Scheme 40 Mechanism for the synthesis of *ortho*-substituted olefinated derivatives of tertiary amines.

cleavage followed by alkene coordination, migratory insertion and β-hydride elimination, similar to Scheme 32.

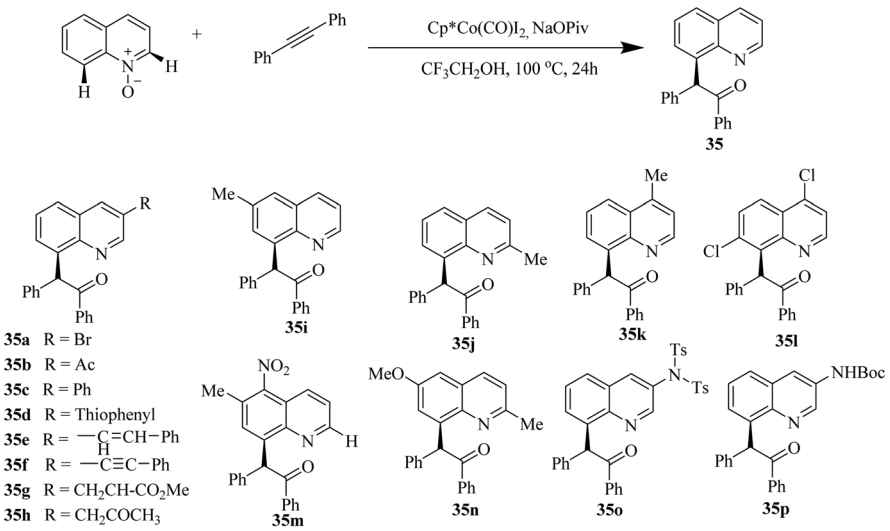
In an analogous publication, Sundararaju developed a new transformation on the C8-position of quinolines using *N*-oxide as a traceless directing group (Scheme 42).[94,95] It was reported that when quinoline-*N*-oxides were subjected to cobalt catalyzed coupling of quinoline with alkynes (**35**) at the C8-position through C–H activation, it was accompanied by intramolecular oxygen transfer in such a way that the reaction afforded C–O coupling, generating quinolines substituted with carbonyl derivatives of alkynes.

In another approach, aniline was converted to its *N*-oxide to serve the purpose of TDG in a rhodium catalyzed C–H activation reaction (Scheme 43).[96] The reaction was carried out with regioselective annulation of tertiary aniline *N*-oxide, which resulted in the generation of *N*-alkyl indoles by tandem C–H activation, oxygen atom transfer and dealkylative cyclization. This unprecedented coupling allowed the generation of alkyl indole derivatives (**36a–p**) in a remarkable step economical and atom economical way with high functional group tolerance and substrate scope. The substrate undergoes *ortho* C–H activation to form a 5-membered cyclometallated species. This species further gives a 7-membered rhodacycle intermediate *via* alkene insertion, which subsequently undergoes reductive elimination of the CO bond followed by oxidative addition to form an enolate intermediate and finally Ag mediated CN cleavage and intramolecular nucleophilic cyclization to give the final desired product.

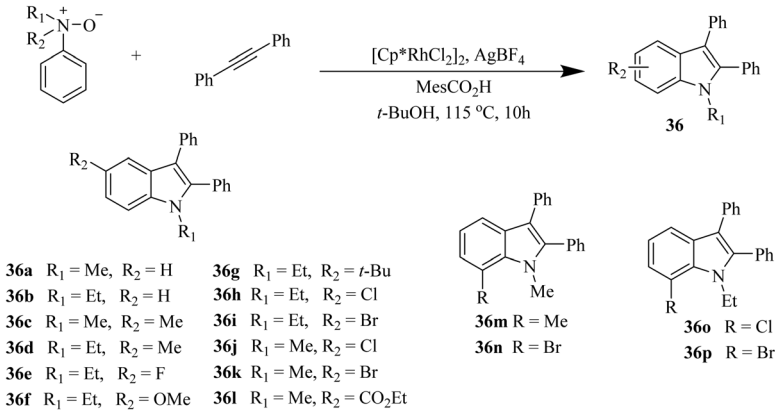
**2.2.2 Nitrones.** Nitrones are electrophilic directing groups which are *N*-oxides of imines.[97,98] These constitute a special class of imines which play an imperative role in C–H activation reactions due to their unique reactivity owing to the polar nature of the N–O bond and electrophilicity of imine moieties.[99,100] The realization of the potential of nitrone as a directing group came into the picture in 2013 with the work of Li. He introduced a strategy for Rh catalyzed access to indenones by means of redox neutral C–H annulative coupling of aryl nitrones with internal alkynes under highly mild conditions (Scheme 44).[101] Aryl nitrones were coupled with diphenyl acetylenes by a rhodium catalyzed C–H activation reaction where ylide nitrones functioned as a directing group. Aryl nitrones substituted with a wide range of electron-withdrawing and -releasing groups underwent smooth coupling with diphenyl acetylenes to form indenones (**37a–w**) in good to moderate yields.



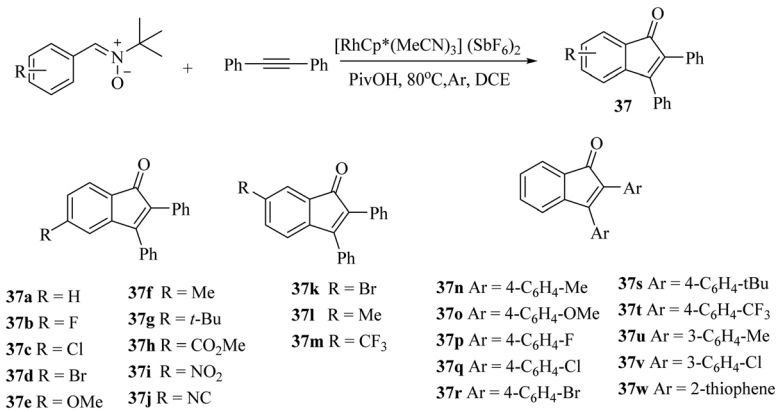

Scheme 41 Rh(III) catalyzed highly selective olefination at the C8-position.




Scheme 42 Cobalt catalyzed coupling of quinoline with alkynes.



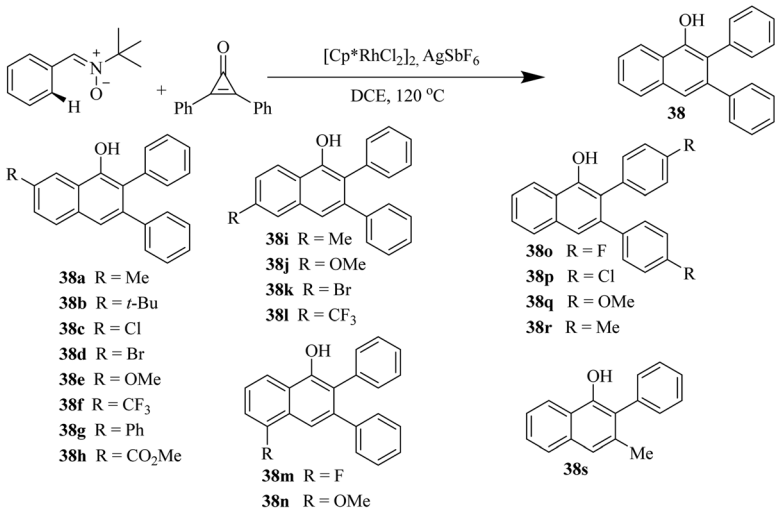

Scheme 43 Rhodium catalyzed regioselective annulation of tertiary aniline *N*-oxide.




Scheme 44 Rhodium catalyzed regioselective annulation of aryl nitrones with internal alkynes.

In 2016, Li and co-workers extended his study to present a common platform for simultaneous discussion of both the effects (Scheme 45).[102] It was reported that by merely controlling the substrate, the 1,3-dipolar nature and traceless directing group feature could be switched, thereby giving access to totally diverse products through two different reactions. It was observed that when *N*-tertiary-butyl nitrones bear a small group such as hydrogen in their *ortho*-position, they underwent a

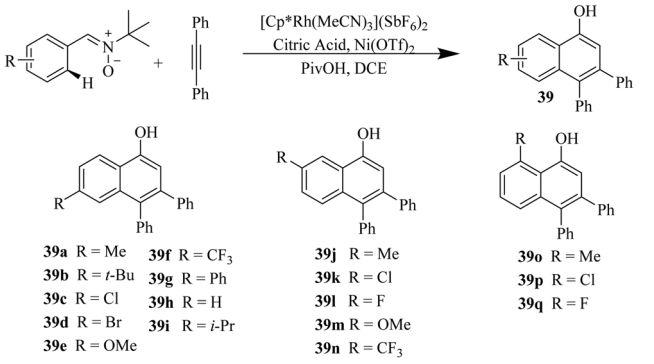



Scheme 45 Rh catalyzed coupling reaction with cyclopropenones.

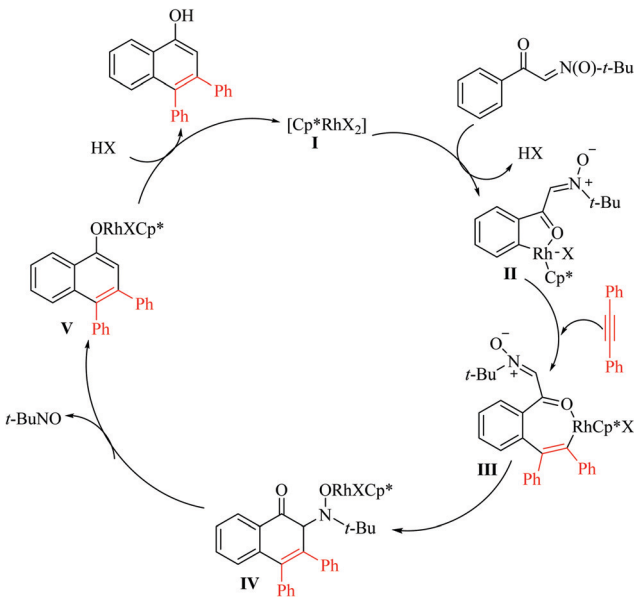
coupling reaction with cyclopropenones through Rh catalyzed C–H activation where the nitrone acted as a traceless directing group. Alternatively, it afforded a [3+2] addition reaction with cyclopropenones following C–H acylation. Both the reactions exhibited high diastereoselectivity, a broad substrate scope and functional group tolerance. The mechanism has been proposed that the reaction begins with cyclometalation followed by coordination and migratory insertion into the imine moiety, followed by β-carbon elimination protonolysis to 1-naphthol (**38a–s**).

Li and his co-workers further reported an analogous synthesis of naphthols (**39a–q**) using nitrones as a traceless directing group but with different substrates (Scheme 46).[103] They resorted to Rh(III) catalyzed efficient and redox neutral C–H activation of α-carbonyl nitrones and an annulation reaction with alkynes, affording access to 3,4-disubstituted naphthols with high regioselectivity and good compatibility with functional groups. Based upon various mechanistic studies carried by Li and co-workers, they further demonstrated a plausible mechanism for this reaction. Nitrone oxygen assisted C–H activation forms a rhodacycle intermediate followed by alkyne coordination and migratory insertion. It was subsequently followed by migratory insertion of a Rh–C alkenyl bond into the imine followed by β-carbon elimination and protonolysis (in the same manner as that of Scheme 38) afforded the desired product (Scheme 47).

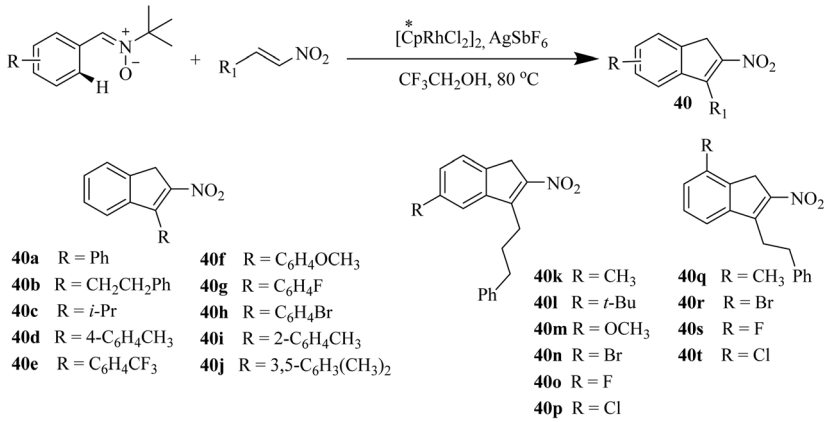
Further, in another application, Li and co-workers have demonstrated the use of nitrones as traceless directing groups for the synthesis of indenes (Scheme 48).[104] They synthesized nitro-functionalized indenes *via* a Rh(III) catalyzed C–H activation reaction of variously substituted *N*-tertiary butyl-α-phenyl-nitrones and annulations of substituted 2-nitroarenes. The reaction delivered the corresponding nitro-indenes (**40a–t**) in good to moderate yields with high regioselectivity and exhibited good functional group tolerance. While exploring the scope of nitroalkenes and nitrones, it was figured out that although the reaction was tolerant to various electron-withdrawing and electron-releasing groups, the reaction efficiency was highly



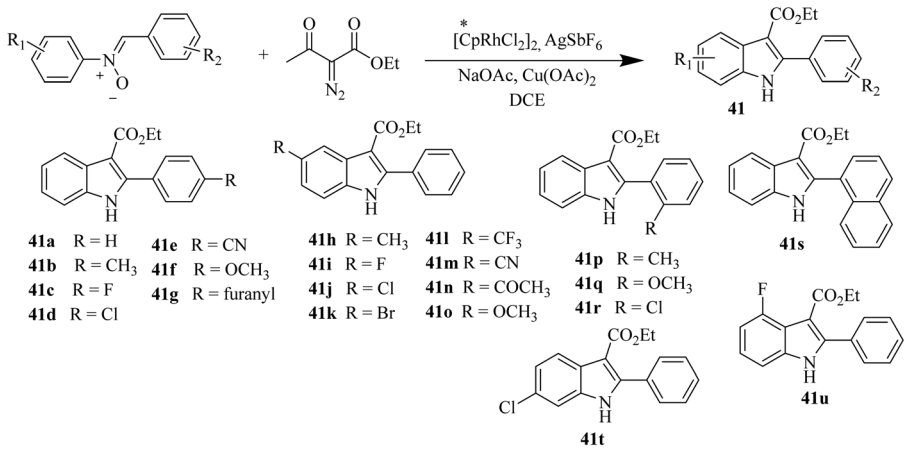

Scheme 46 Rh(III) catalyzed redox neutral synthesis of naphthols.




Scheme 47 Mechanism for redox neutral synthesis of naphthols.




Scheme 48 Rh(III) catalyzed synthesis of nitro-functionalized indenes.




Scheme 49 Rh(III) catalyzed synthesis of 2,3-disubstituted NH indoles.

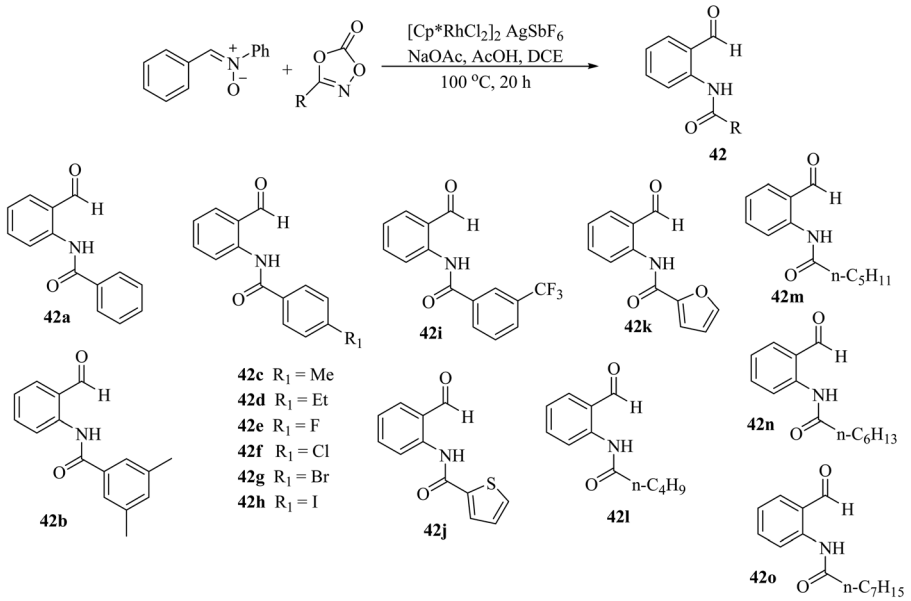
influenced by electronic effects. To illustrate the synthetic application of the product formed by annulation, it was subjected to a derivatization reaction. It was subjected to reduction in the presence of RANEY®-nickel, which gave a ketone derivative of indene in good yield.

In 2017, Chen and co-workers carried out a one pot mild and efficient synthesis of 2,3-disubstituted NH indoles (Scheme 49). They carried out a rhodium-catalyzed C–H functionalization and annulation reaction by intermolecular coupling between aryl nitrones and diazo compounds to furnish structurally diverse 2,3-disubstituted NH indoles (**41a–u**) with high regioselectivity in high yields.[105] Nitrones bearing different *N*-aryl substituents were used in the reaction to examine the substrate scope of the reaction. It was observed that the *N*-aryl moiety substituted with different electron-releasing and -withdrawing groups resulted in good yields. Substituents such as methyl, fluorine, chlorine, bromine, methoxy, trifluoromethyl, and even acetyl groups at the *para*-position resulted in excellent yields of compounds, while the cyano group resulted in slightly lower yields. However, a highly regioselective product was formed in the case of the *meta*-methyl substituted substrate and good yields were obtained for *ortho*-substituted substrates.

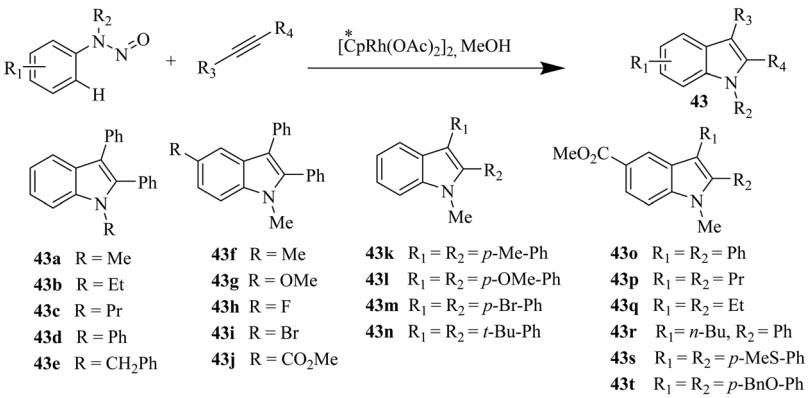
In 2017, Wang and his co-workers developed novel access to functionalized aryl aldehydes by Rh catalyzed C–H activation using nitrones as a directing group. They carried out synthesis of functionalized aryl aldehydes (**42a–o**) by using site selective amidation of aryl nitrones with 1,4,2-dioxazol-5-ones in the presence of a Rh catalyst (Scheme 50).[106] To examine the effect of the substituents on the reaction, a variety of 3-aryl-1,4,2-dioxazol-5-ones were subjected to the standard conditions of the reaction. It was observed that on incorporating F, Cl, Br and I groups on the aryl moiety of 3-aryl-1,4,2-dioxazol-5-ones, the reaction proceeded smoothly with good yields of the products, but substituting with Me and OMe groups resulted in a decrease in yields. To investigate the synthetic potential of the amidated product, several transformations were made to form the olefinated product, amino benzaldehyde and cyclized product.

**2.2.3 *N*-Nitroso group as a traceless directing group.** The *N*-nitroso group is among the novel directing groups which are highly appealing to researchers due to some of its exceptional characteristics.[107] It has excellent potential to interact with transition metals and thus can play the important role of a directing group to effect metal catalyzed C–H activation reactions.[108]




Scheme 50 Rh(III) catalyzed site selective amidation of aryl nitrones.

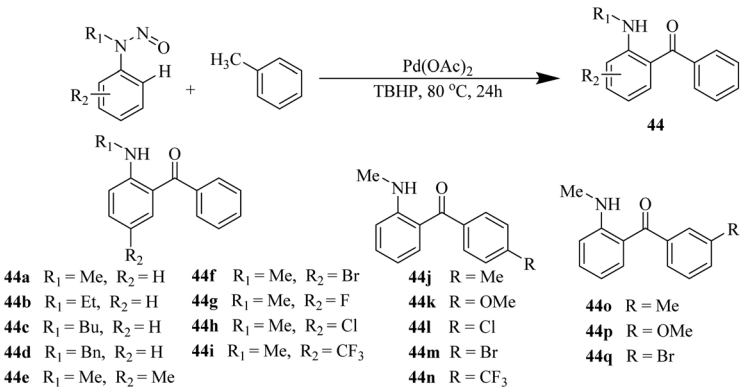



Scheme 51 Synthesis of *N*-alkyl indoles *via* nitroso directed annulation.

It normally occurs in the form of *N*-nitrosoamines (*e.g.* *N*-nitroso anilines) where the nitroso group serves as an internal oxidant and directing group in cascade C–H activation and annulation reactions to furnish diversified heterocyclic scaffolds such as indoles, quinolines *etc.*[109] It has also adopted a traceless character through a distinct electrophilic directing group removal strategy.

One of the earliest approaches where this remarkable ability of the *N*-nitroso group has been applied is the synthesis of *N*-alkyl indoles (**43a–t**) through a simple protocol given by Wang and Huang in 2013 (Scheme 51).[110] They developed a novel redox neutral Rh catalyzed reaction between nitrous amides and acetylenes where C–H activation and annulation were performed in a sequential manner using *N*-nitroso as a traceless directing group. The reaction displayed remarkable features such as high regioselectivity, excellent yields, and high functional group compatibility, with no requirement for an external oxidant or additives, and a wide substrate scope. This tempted researchers to attempt more such reactions involving traceless nitroso directed C–H activation and annulation reactions resulting in the formation of various heterocyclic scaffolds. Based on competitive experiments and kinetic isotope studies, it has been revealed that in this transformation, C–H activation proceeds through a Concerted Metalation-Deprotonation (CMD) mechanism. Then, the resulting Rh species undergoes binding to alkyne followed by 1,2-*cis* addition. Out of these two steps, it is still unclear which proceeds first. Following this, the reaction undergoes reductive elimination and ring contraction of the metallacycle intermediate to afford the target compound. However, the detailed mechanism is still unclear.

Soon after the development of the *N*-nitroso group as a directing group, Luo and his co-workers developed a Pd-catalyzed C–H activation involving a cross coupling reaction between *N*-nitrosoanilines and various derivatives of toluene for the synthesis of *N*-alkyl-2-aminobenzophenones (**44a–q**) (Scheme 52).[111] The reaction occurred through *ortho*-acylation

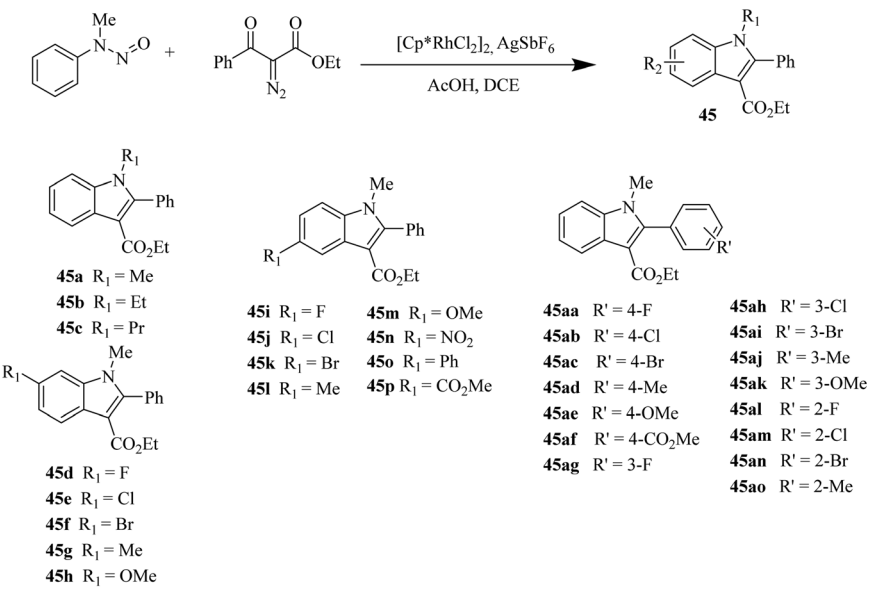



Scheme 52 Pd catalyzed cross coupling reaction between *N*-nitrosoanilines and derivatives of toluene.

of *N*-nitrosoanilines where an effective acyl precursor was delivered by toluene, which was directed by the nitroso functional group. The reaction was compatible with a wide number of substituents such as chloro, fluoro, methoxy *etc.* at different positions of *N*-nitrosoamines and toluene, delivering the target products in high yields. The exact mechanism of this transformation remained yet unclear.

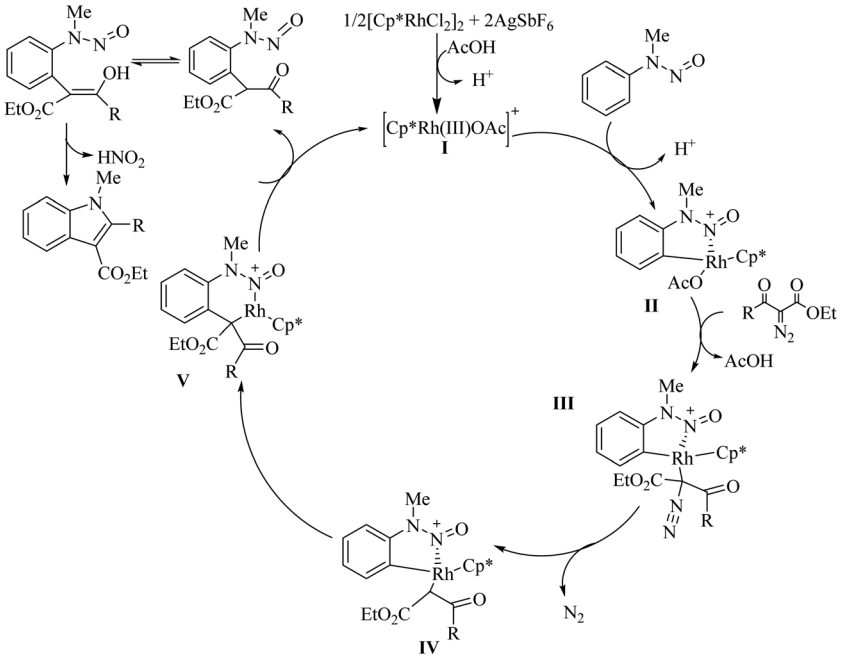
Zhu and co-workers have used a distinct electrophilic DG removal strategy with *N*-nitosoanilines (Scheme 53).[112] They performed a highly selective Rh(III) catalyzed synthesis of indoles through a traceless, atom- and step-economic, cascade approach. The reaction was performed with easily accessible *N*-nitrosoanilines and α-diazo-β-keto compounds, which involved C–H activation through cyclization and denitrosation in a tandem manner. It was observed that the reactivity was highly influenced by the bulkiness of the *N*-substituent with respect to the fact that the substrates bearing small substituents on the N atom (such as ethyl and methyl groups) delivered the products in excellent yields as compared to the lower yields given by bulky substituents (isopropyl). It was also influenced by factors such as the steric hindrance and electronic properties of arenes where the yield may vary. Amines substituted at the *ortho*-positions delivered lower yields of the product as compared to both *meta*- and *para*-substituted nitosoanilines. Moreover, it was also influenced by electronic effects as the nitosoanilines substituted with electron rich substituents such as Me and OMe groups showed higher reactivity as compared to the ones substituted with electron withdrawing substituents such as halogens, $CO_2Me$, $NO_2$ and phenyl groups.

The reaction is proposed with the interaction of a Ag salt and $[RhCp^*Cl_2]_2$ through a ligand exchange method to deliver the catalytically active Rh(III) species. *N*-Nitrosoaniline undergoes C–H activation with the active Rh(III) species to form a rhodacycle intermediate, which undergoes coordination with diazo-compounds accompanied by $N_2$ release to form Rh(III) carbene followed by migratory insertion, protodemetalation, tautomerization and cyclization through de-nitrosation to afford the final indole products (Scheme 54).

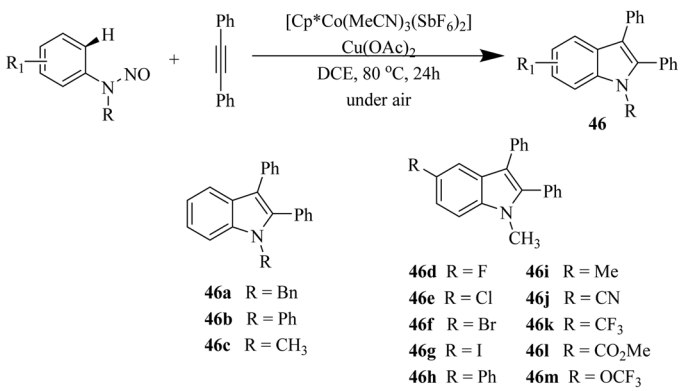



Scheme 53 Rh(III) catalyzed tandem cyclization and denitrosation.



Scheme 54 Mechanism for Rh-catalyzed synthesis of indoles.

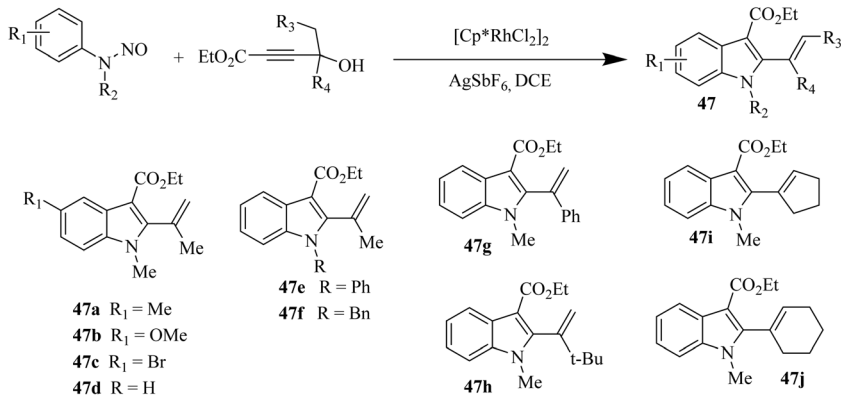


Scheme 55 Cobalt(III) catalyzed synthesis of indoles from nitrosoanilines.

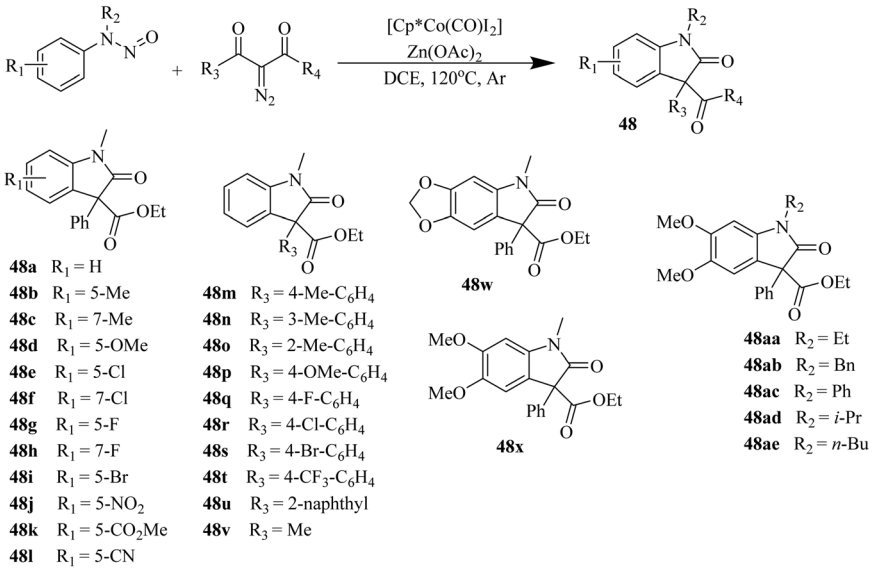
Later, in the same year, Liang and Jiao also carried out synthesis of indoles (**46a–m**) from nitrosoanilines (Scheme 55).[113] Cobalt(III) catalyzed highly selective redox neutral coupling of alkynes was performed with *meta*-substituted nitrosoanilines by cyclization through C–H activation *via* the CMD mechanism. The most distinctive feature of the reaction was the reactivity even with electron deficient internal alkynes, which was not observed with the [Cp*Rh$^{III}$]-catalyzed system, and high regioselectivity when unsymmetrical *meta*-substituted *N*-nitrosoanilines were used. The reaction proceeded with the generation of an active form of cobalt, which assisted in C–H activation and forms a 5-membered metallacycle intermediate followed by alkyne insertion. Finally, an intramolecular substitution reaction was carried out, which allows simultaneous formation of C–N and cleavage of N–N bonds, resulting in the formation of the desired indole derivatives.

In 2018, Fan along with his co-workers also carried out a novel and effective synthesis of indoles (**47a–j**) from nitrosoanilines and propargyl alcohols through a cobalt catalyzed redox neutral cyclization reaction (Scheme 56).[114] It occurred through simultaneous intramolecular amination/cyclization, NO extrusion, and dehydration. The reaction was observed to be highly compatible with various substituents such as methyl, methoxy, fluoro, chloro, bromo, cyano, and trifluoromethyl groups attached to the phenyl ring of nitrosoanilines, thus allowing facile incorporation of these groups onto the indole nucleus and making possible auxiliary structural transformations. The reaction delivered low yield in the case of *ortho*-substituted substrates, supporting the fact that it is sensitive to steric hindrance.

Zeng and co-workers reported the synthesis of quaternary 2-oxindoles using cobalt(III)-catalyzed efficient cross coupling/cyclization of *N*-nitrosoanilines and α-diazo-β-ketoesters through the combination of a C–H activation strategy with the Wolff rearrangement process (Scheme 57).[115] The unique combination of both the strategies enabled rapid construction




Scheme 56 Cobalt catalyzed redox neutral coupling cyclization reaction.




Scheme 57 Cobalt catalyzed synthesis of 3,3-disubstituted 2-oxindoles.

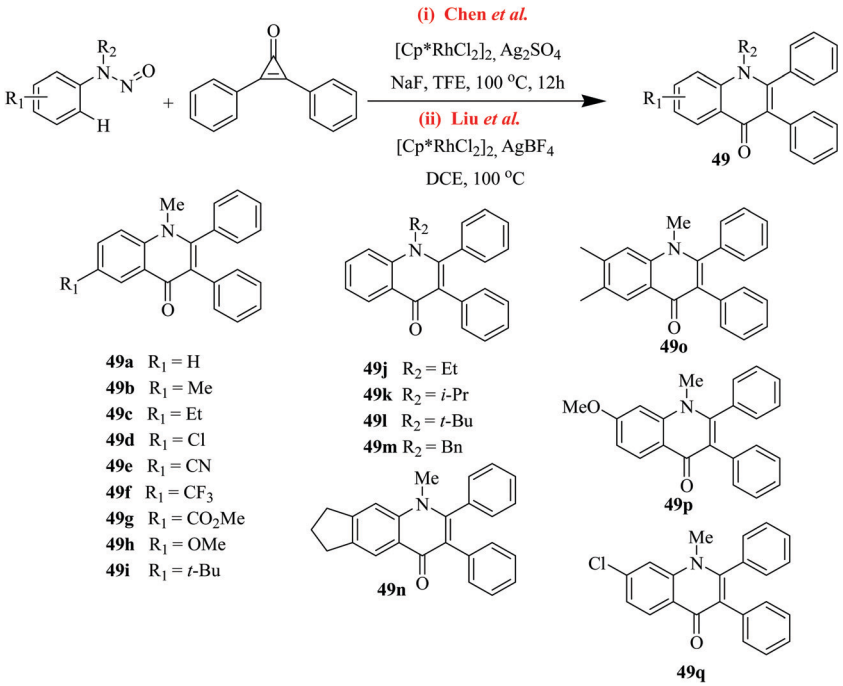
of quaternary 2-oxindoles (**48a–x** and **48aa–ae**) through trapping of a ketene intermediate with cobalt metallocycles. While exploring the substrate scope of cobalt(III)-catalyzed synthesis of 3,3-disubstituted-2-oxindoles, it was figured out that the reaction displayed an exceptional tolerance for a wide array of functional groups. The reaction delivered high yields of products with electron donating groups (such as Me and OMe) and halides (such as F, Cl and Br). The reaction proceeded smoothly with electron-withdrawing groups (such as CN, $NO_2$ and $CO_2Me$) too but the yields obtained were relatively low as compared to the former cases. Besides, monosubstituted substrates, and 3,4- and 2,3-disubstituted anilines also delivered products in good to moderate yields.

Very recently, two analogous approaches for the synthesis of functionalized 4-quinolones (**49a–q**) were introduced by two groups independently with very slight modifications. In the first approach of Chen and co-workers (2019), highly functionalized 2,3-disubstituted-4-quinolones were synthesized using a Rh(III) catalyzed annulation reaction of *N*-nitrosoanilines and cyclopropenones using *N*-nitroso as a directing group (Scheme 58i).[116] It was observed that the reaction exhibited good regioselectivity using unsymmetrical *meta*-substituted *N*-nitrosoanilines and was compatible with functional groups delivering products in high yields. The second approach involved a similar synthesis of 4-quinolones by the group of Liu (Scheme 58ii).[117] Although it was similar to Chen's study, it displayed a broad substrate scope as compared to Chen. Moreover, it enabled efficient synthesis of 4-quinolones in a much shorter time without the use of additional additives.

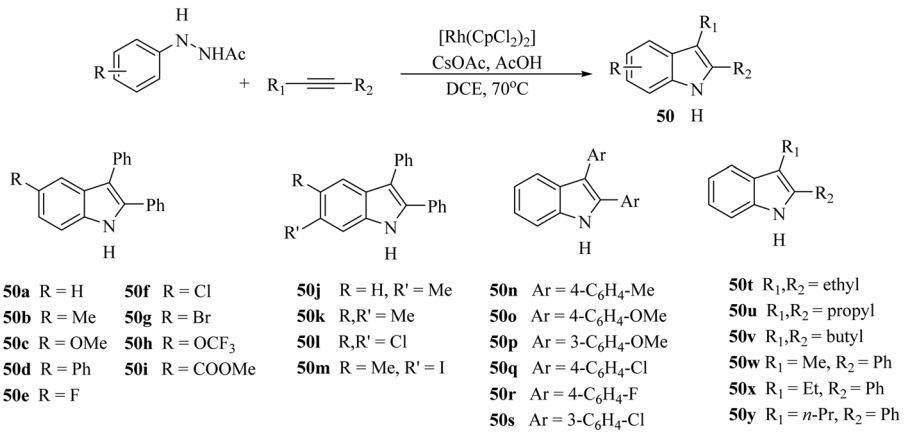
### 2.3 N–N bond based traceless directing groups

N–N bonds can also direct C–H activation by the same mechanism as N–O bonds by simultaneously serving as an internal oxidant and a traceless directing group. Generally, the N–N bond is less labile than the N–O bond due to the partial double bond character. Thus, researchers began to shift their interest towards more labile N–N bond containing groups such as hydrazine and *N*-amino groups by virtue of the weak nature of its single bond. It has eliminated the reliance on the amide bond for an increase in



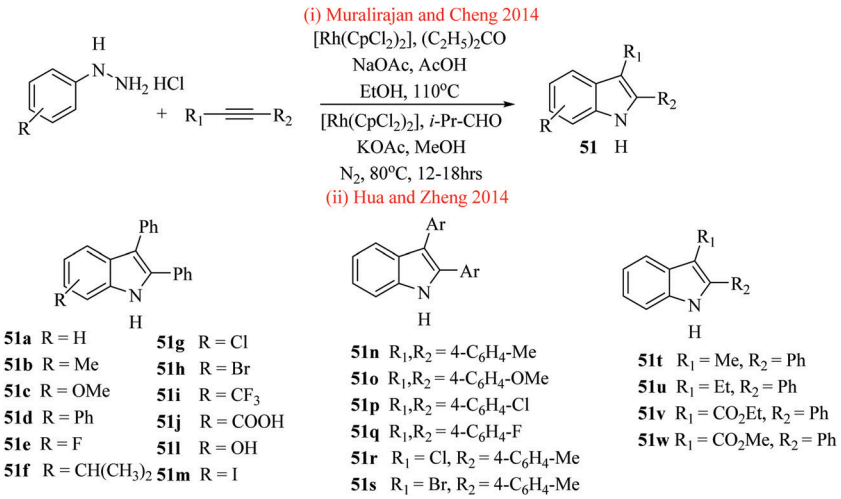

Scheme 58 Annulation reaction of *N*-nitrosoanilines and cyclopropenones using *N*-nitroso as a directing group.



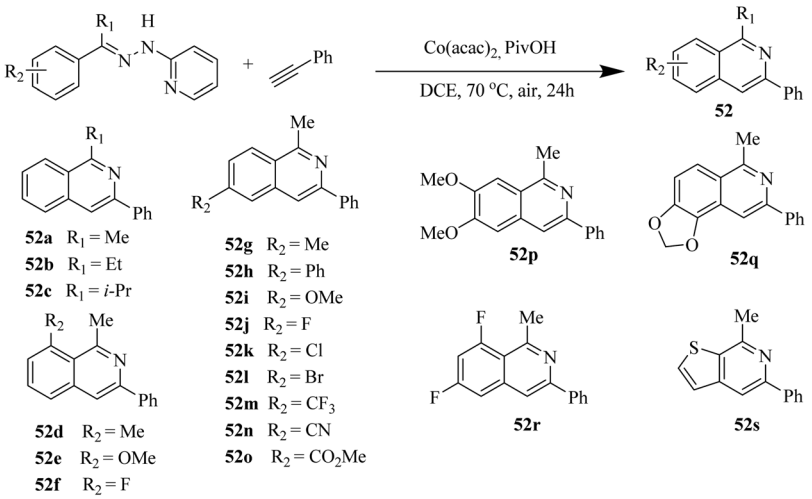

Scheme 59 Rh catalyzed redox neutral coupling of *N*-arylhydrazines with internal alkynes.

proton acidity unlike the N–O bond. One of the earliest uses of the *N*-amino group for transition metal catalyzed C–H activation began with the work of Glorius in 2013 (Scheme 59).[118] He developed a Rh catalyzed traceless strategy for the synthesis of indole (**50a–y**) which served as a potential alternative to Fischer's indole synthesis. The synthesis proceeded through Rh(III) catalyzed redox neutral C–H activation and coupling of *N*-arylhydrazines with internal alkynes. The reaction proceeded in a highly regioselective manner with a broad substrate scope and functional group tolerance.

This was followed by another Rh(III) catalyzed hydrazine directed redox neutral synthesis of indoles. In 2014, Muralirajan and Cheng developed a novel method in which an oxidizing N–N directing group was generated *in situ* during the reaction. It was found that *N*-arylhydrazines generate this oxidizing directing group *in situ* on reacting with diethylketone in the presence of a mild base (NaOAc), which subsequently assists C–H activation of this moiety with internal alkynes at the *ortho* position, leading to the final product formed by reductive elimination (Scheme 60i).[119] The reaction is highly tolerant to a wide variety of functional groups. It was observed that the reaction occurred in a highly regioselective manner and that too without the need for an external oxidant. A somewhat similar approach was used by Zheng and Hua in 2014 in which a hydrazone group, generated *in situ*, assisted in Rh(III) catalyzed C–H activation of *N*-aryl hydrazines with alkynes (Scheme 60ii).[120] *N*-Arylhydrazine chloride on reaction with any CO source generates an autocleavable and autoformed




Scheme 60 Rh(III) catalyzed hydrazine directed redox neutral synthesis of indoles.



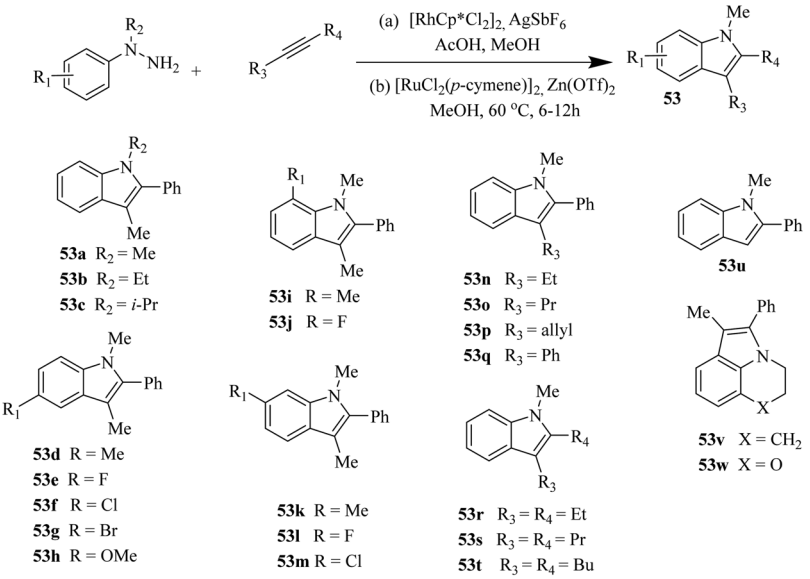

Scheme 61 Co-Catalyzed synthesis of isoquinoline.

hydrazone group *in situ* which directs *ortho*-activation in similar way to that of Cheng. Various CO sources such as acetone, cyclohexanone, cyclopentanone, isobutylaldehyde *etc.* can be used for the generation of oxidizing directing groups but isobutylaldehyde resulted in excellent yields.

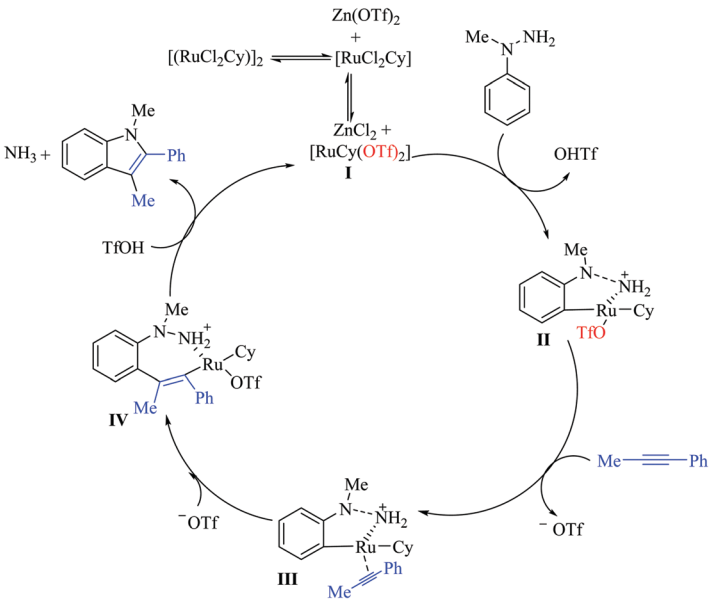
The synthesis of heterocycles through C–H activation was only reported with monodentate systems until an innovative Co-catalyzed synthesis of isoquinoline was carried out by Zhu and co-workers (Scheme 61).[121] They have broken all stereotypes of using monodentate systems by carrying out the first bidentate directed traceless, highly reactive and selective synthesis of isoquinolines (**52a–s**) *via* 2-hydrazinyl pyridine directed C–H coupling/cyclization with terminal alkynes. It was inferred that the efficiency was affected inversely with respect to the bulkiness of the alkylidiene group from the fact that the yield gradually falls on moving from ethylidiene to propylidiene and further to butylidiene.

In another publication in the same year, Zhu has synthesized olefinated indoles (**53a–w**) through a traceless N–N bond based Rh(III) catalyzed C–H activation approach using arylhydrazines and acrylates as starting materials (Scheme 62).[122] The reaction proceeded in a highly regioselective manner at room temperature, having low catalyst loading with high step and atom economy of the overall transformation, and exhibited appreciable functional group tolerance. In another publication, he reported the synthesis of indoles from *N*-hydrazines and alkynes using a ruthenium catalyst instead of a rhodium catalyst through an almost similar reaction under relatively mild conditions in an excellent step and atom economical pathway with a wide range of substitutions.[123] The latter eliminated the use of the unstable acid additive which was required in the Rh(III) catalyzed method. The reaction evidenced the superior adaptability of Ru(III) systems due to their excellent ability of incorporation of dialkyl substituted alkynes and olefination. The reaction begins with the usual generation of catalytically active Ru(III) species from the reaction of $[RuCl_2(p\text{-cymene})_2]$ and $Zn(OTf)_2$ followed by *ortho* C–H activation to form a 5-membered ruthenacycle intermediate. This intermediate subsequently undergoes alkyne coordination




Scheme 62 Synthesis of indoles from *N*-hydrazines.

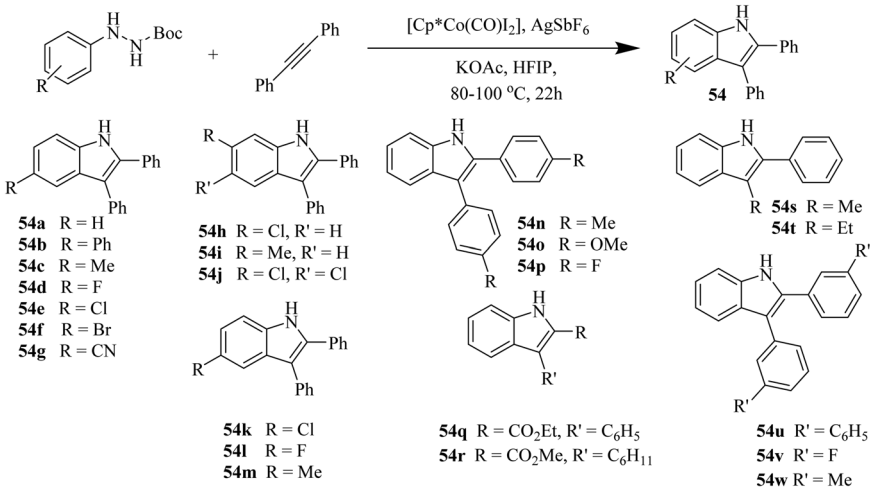



Scheme 63 Mechanism for the synthesis of indoles from *N*-hydrazines.

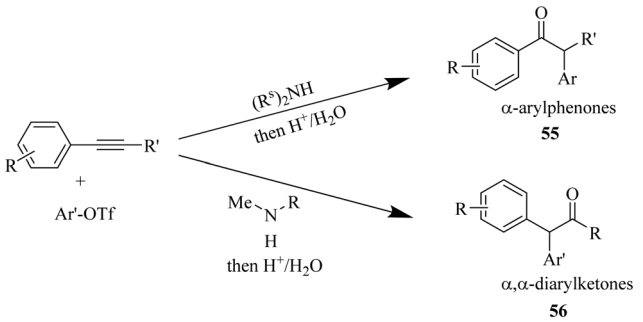
and migratory insertion, leading to the formation of a 7-membered ruthenacycle intermediate, which subsequently undergoes β-hydride elimination and ring closure to form the desired product (Scheme 63).

Glorius and co-workers have also synthesized indoles (**54a–w**) in the same year but with an unprecedented redox neutral coupling of *N*-Boc protected hydrazines with alkynes through a cobalt catalyzed C–H activation reaction (Scheme 64).[124] The substrate scope of the reaction was explored with both the substrates and it was observed that the reaction was highly tolerant to both electron-withdrawing and electron-donating substituents present on *N*-Boc protected hydrazines, whereas high regioselectivity was observed for *meta*-substituted *N*-Boc aryl hydrazines. Moreover, some *ortho*-substituted *N*-Boc aryl hydrazines which showed almost negligible reactivity with Rh(III) delivered the desired products in excellent yields through this Co-catalyzed catalytic methodology. Thus, it was concluded that the reactivity was superior in Co-catalyzed reactions as compared to the Rh(III) catalyst when *ortho*-substituted Boc-protected hydrazines were used.

In 2018, amines were used for the traceless directing approach but this time they were not used for their internal oxidant property neither in the *N*-nitroso and nitrone form nor in the *N*-amine form (Scheme 65).[125] The reaction was achieved through three




Scheme 64 Synthesis of indoles through coupling of *N*-Boc protected hydrazines with alkynes.

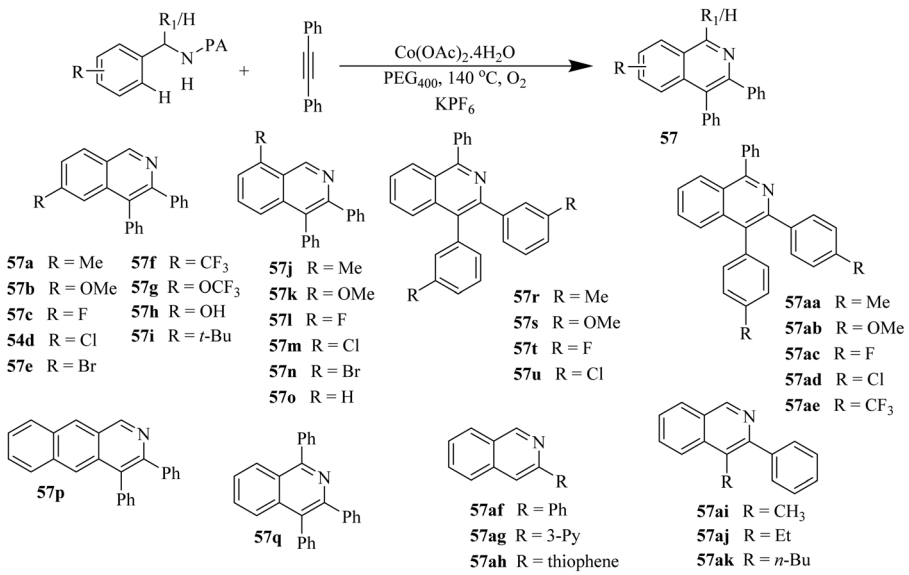



Scheme 65 Three component arylation of alkynes.

component arylation of alkynes to form α-arylphenones (**55**) or α,α-diarylketones (**56**) through the formation of an enamine intermediate that hydrolyzed to give the target products.

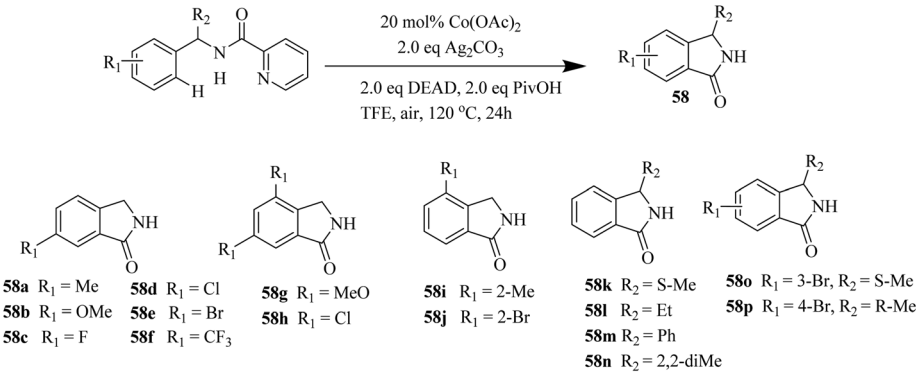
### 2.4 Bidentate amide bond based traceless directing groups

The use of *N*,*N*-bidentate based amide directing groups for C–H activation reactions gained momentum after the landmark contribution of Dauglis, who has first introduced amides of quinolone and picolinic acids for directing the substitutions. These are bi-coordinated species bearing two nitrogen atoms that coordinated with the metal centre to form a cyclic intermediate.[126] Moreover, their ease of installation and removal gave additional advantages. But the traceless character of the picolinamide moiety was first realized by Cui and his co-workers in 2017 (Scheme 66).[14] The group used picolinamide as a traceless directing group with a cobalt catalyst for highly regioselective synthesis of isoquinolines (**57a–u, aa–ak**) through an oxidative annulation reaction between benzylamides and alkynes. The reaction demonstrated a broad substrate scope and functional group compatibility. The additional advantage




Scheme 66 Regioselective synthesis of isoquinolines.



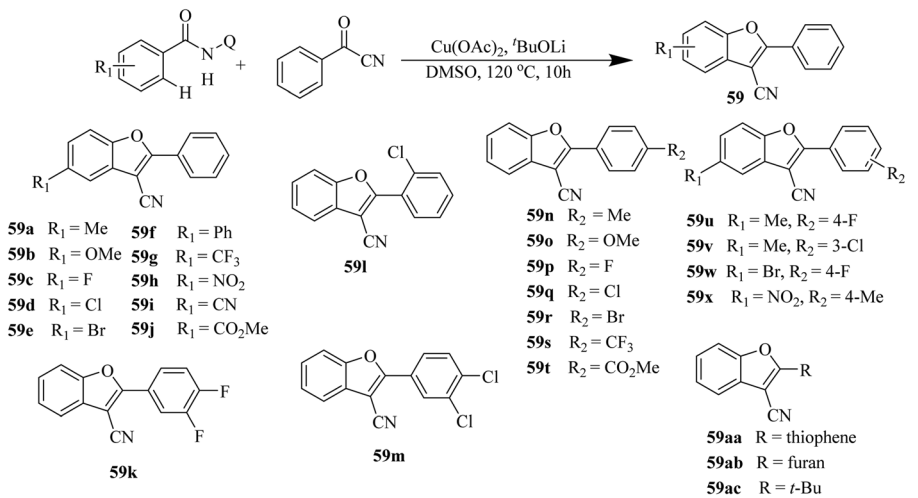

Scheme 67 Cobalt catalyzed carbonylation of benzylamines.

of this reaction is that besides internal aliphatic and aromatic alkynes, terminal alkynes could also be used in this transformation. Moreover, no metal oxidant was required in these reactions, while oxygen itself was used as the sole terminal oxidant.

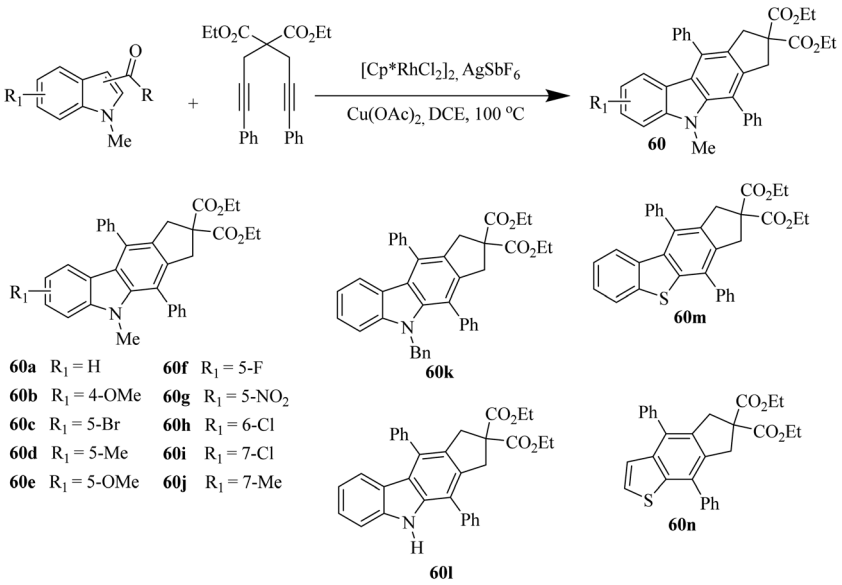
Zhong and co-workers carried out the synthesis of various isoindolinones (**58a–p**) by cobalt catalyzed carbonylation of benzylamines where azodicarboxylates were used as a carbonyl source (Scheme 67).[127] It was observed that this benign carbonylation strategy was highly compatible with a wide range of aromatic and heteroaromatic substituted amines, affording the desired corresponding products with good to moderate yields. It was the first cobalt catalyzed traceless directing group assisted C–H carbonylation that has application for formal synthesis of (+) garenoxacin.

Recently, in 2019, Zhang and co-workers presented a copper mediated simultaneous construction of C–C and C–O bonds in a one pot fashion to enable the synthesis of 2,3-disubstituted benzofurans (**59a–x**, **aa–ac**) from benzamides and benzoyl acetonitriles by using the assistance of an 8-aminoquinolyl auxiliary as a traceless directing group (Scheme 68).[128] The reaction proceeded through first *ortho*-arylation of benzamide with benzoyl acetonitriles followed by subsequent cleavage of C–C and formation of C–O bonds simultaneously at the same position where the amide bond was present. It was observed that the reactivity was unaffected by electronic effects on the benzene rings due to the fact that both electron-withdrawing and -releasing substituents delivered products in good to moderate yields. However, steric hindrance influenced negatively the rate of the reaction and the transformation could be extended only up to propanenitriles. On extending it further to butanenitriles, the reaction failed to occur.

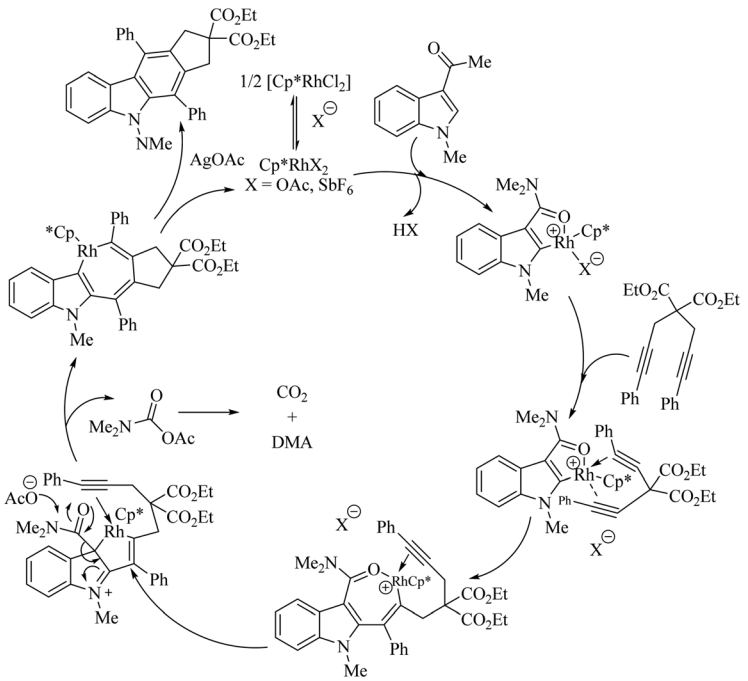
Very recently, in 2020, Wang and his co-workers carried out cascade C–H/C–C bond cleavage and cyclization reactions to allow the synthesis of cyclopenta[*b*]carbazoles (**60a–n**) under the assistance of an amide directing group (Scheme 69).[129] They carried out a Rh(III) catalyzed reaction between amide substituted indoles and diynes which involved C–C bond cleavage *via* a retro Friedel–Craft approach. The reaction proceeded with generation of active Rh(III) species formed through *in situ* ligand exchange with Ag salts followed by metalation of the amide substituted indoles through C–H activation. Then, one alkyne unit of diyne undergoes coordination and migratory insertion on the intermediate (formed through C–H activation) to form a seven membered intermediate. Further, formation of the Rh–C bond takes place *via* indole dearomatization during




Scheme 68 Synthesis of 2,3-disubstituted benzofurans from benzamides and benzoylacetonitriles.




Scheme 69 Rh(III) catalyzed cascade reaction between amide substituted indoles and diynes.



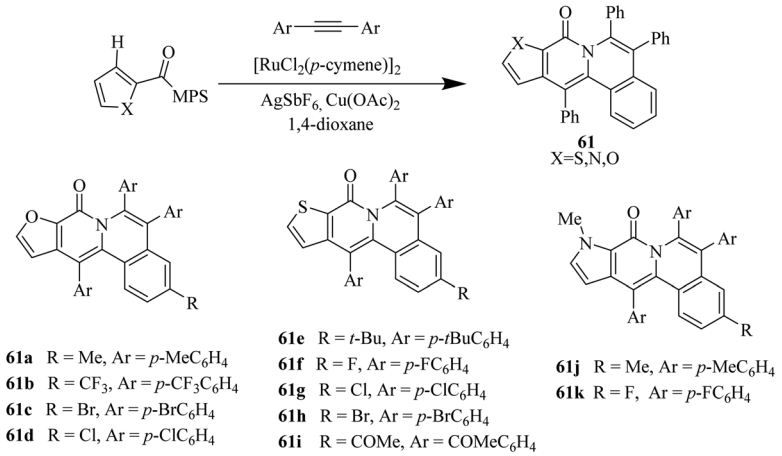

Scheme 70 Mechanism for the cascade reaction between amide substituted indoles and diynes.

weak interaction of the second alkyne unit of diyne, making it act as a bidentate ligand. This was followed by simultaneous cleavage of the C–C bond and migratory insertion of this second alkyne unit, which was weakly coordinated to form a seven membered intermediate. This was subsequently followed by reductive elimination to generate cyclopenta[*b*]carbazoles (Scheme 70).

### 2.5 S=O bond based traceless directing groups

Sahoo and co-workers developed a novel strategy of an unsymmetrical annulation reaction of heteroaryls with two distinct alkynes under the assistance of a Methyl Phenyl Sulfoximine (MPS) directing group (Scheme 71).[130] Functionalization of multiple C–H bonds was achieved with removal of the directing group in a one pot fashion. The reaction proceeded through double annulation of heteroaryl compounds with both symmetrical and unsymmetrical alkynes by using a Ru-catalyst to enable the synthesis of highly complex π-conjugated heteroaryl fused polycyclic amide scaffolds by the virtue of MPS. The C–H bonds were functionally transformed into two C–C and two C–N bonds in a single operation with high substrate scope and functional group compatibility. Mechanistic details of this transformation are yet to



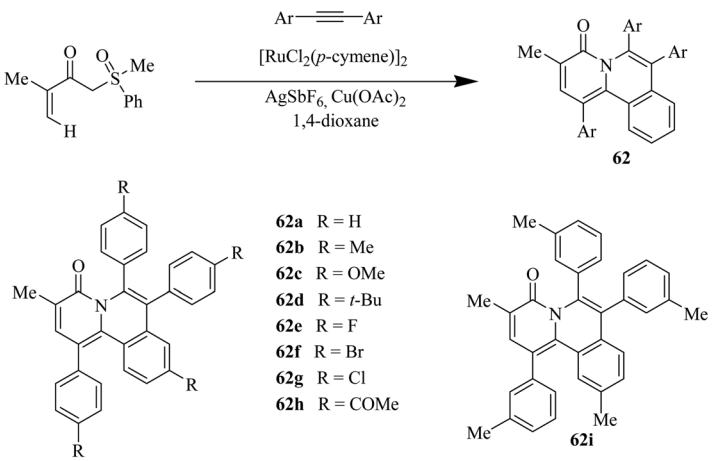

Scheme 71 Ru-Catalyzed double annulation reaction.

be established but a plausible outline suggests that it follows a sequence of reactions. It proceeds with the activation of the catalyst *via* ligand exchange, which activates the *ortho* C–H bond of the heteroaryl moiety. This was subsequently followed by alkyne coordination and migratory insertion, thereby resulting in the mono-annulated product, which is followed by a second annulation reaction that provides the desired polycyclic fused heterocycles (**61a–k**).

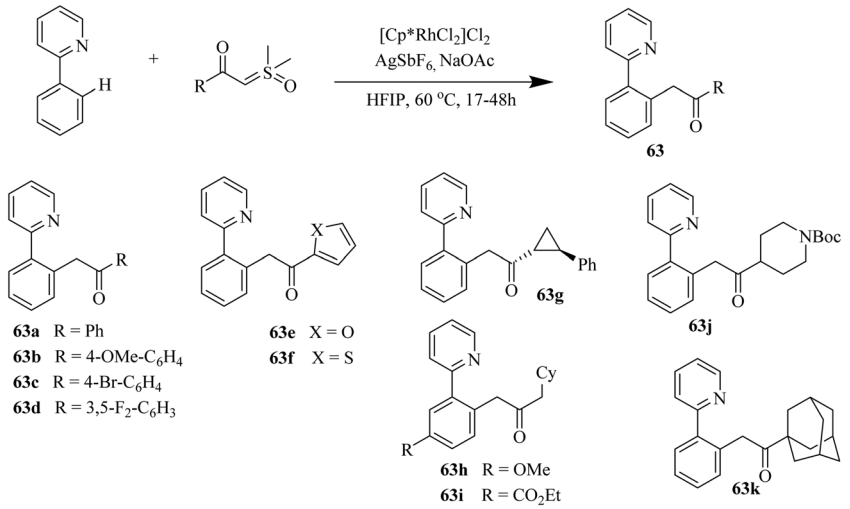
Analogous to these, Sahoo and co-workers carried out similar multiple C–H bond activation under exactly the same reaction conditions, creating two C–C and two C–N bonds in a single operation (Scheme 72).[131] The only difference was the use of an acrylic acid substrate that enables fabrication of pyrido-fused-isoquinolines (**62a–i**). Thus, MPS succeeds in promoting double annulation of acrylic acids with alkynes in a one pot fashion under Ru-catalytic conditions. Moreover, the synthetic adaptability of this methodology has gained importance and validation by virtue of its ability to recover methyl phenyl sufoxide, a precursor of MPS. To further validate this method on more molecular scaffolds, they envisaged double annulation of a benzopyran system, *viz.*, 2*H*-chromene carboxylic acid, as it is present in a large number of biologically active scaffolds. They succeeded in this attempt of double annulation, delivering products in good to moderate yields.

The potential of sulfoxonium ylide to assist regioselective C–H activation as a traceless directing group was first realized by Aïssa and co-workers in 2017 (Scheme 73).[132] They carried out cross coupling of C($sp^2$)–H bonds of arenes and heteroarenes with α-carbonyl sulfoxonium ylides in the presence of a rhodium catalyst. The reaction proceeded through C–H activation followed by insertion of sulfoxonium ylide and finally protodemetalation to furnish acridines (**63a–k**). The protodemetalation served as a turn over limiting step. Hexafluoroisopropanol (HFIP) seemed to be essential for efficient protodemetalation, responsible for both catalyst turnover and product delivery. It was observed that the reaction could take place even in the absence of a base, but adding the base into the reaction leads to a transformation thereby delivering high yields of various acridine derivatives.

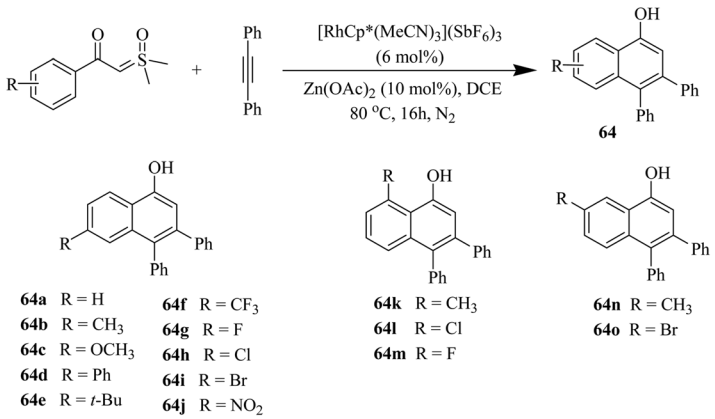
In 2017, Li and co-workers carried out redox neutral annulation of sulfoxonium ylides with diarylacetylenes to afford 1-naphthols *via* a C–H activation pathway (Scheme 74).[133] The reaction proceeded under the assistance of sulfoxonium ylide as a traceless




Scheme 72 Ru-Catalyzed synthesis of pyrido-fused isoquinolines.




Scheme 73 Rh(III) catalyzed cross coupling of arenes with α-carbonyl sulfoxonium ylides.

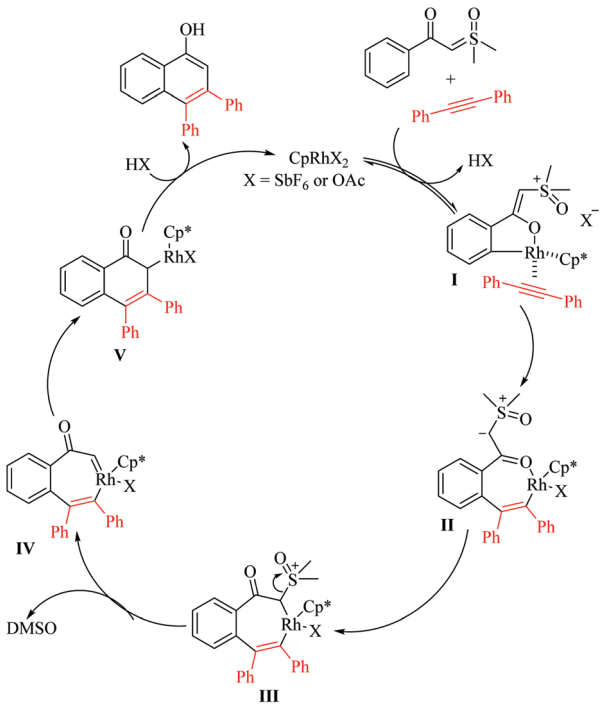



Scheme 74 Redox neutral annulation of sulfoxonium ylides with alkynes.

directing group in a highly selective manner under mild conditions to yield 1-naphthols (**64a–o**) in good to moderate yields. While examining the substrate scope of diarylacetylenes bearing both electron-releasing and electron-withdrawing groups at the 4th position, they efficiently underwent smooth annulation, affording high yields of products. Moreover, couplings occurred smoothly for *meta*-fluoro and *meta*-methyl substituted diarylacetylenes too. Both symmetrical and unsymmetrical alkynes were compatible with good to excellent regioselectivity. To confirm the synthetic applicability of the reaction, gram scale reactions were performed and it was observed that the product was isolated in very good yields. In addition, the quick conversion of naphthols into triflates led researchers to the opinion that this could be employed as a fabricant in transition metal catalyzed cross couplings (Scheme 75). The oxygen atom of the sulfoxonium substrate coordinates with the metal atom to undergo cyclometalation and forms 5-membered rhodacyclic intermediate **I**, to which the alkyne substrate undergoes alkyne insertion to afford 7-membered rhodacyclic intermediate **II**. This intermediate subsequently tautomerizes to form another intermediate **III**, which further on α-elimination produces α-oxo carbenoid species **IV**. Insertion of a Rh–alkenyl bond into this α-oxo carbenoid species **IV** forms **V**, which undergoes protonolysis to form the final product.

Diazo precursor dimerization is well known with several literature reports, but their couplings deliver a mixture of all the three possible coupling products without any selectivity for the desired product, which is not a synthetically efficient process.[134–138] On the other hand, dimerization of sulfoxonium ylides has never been reported directly due to the fact that although they are more nucleophilic than the diazo analogues the decomposition to metal carbene occurs at a very slow rate, making their coupling a difficult task to perform.[139] Thus, Maulide and co-workers came up with a novel idea that a metal carbene will be formed readily from a diazo precursor and this carbene will be attacked more selectively by a highly nucleophilic sulfoxonium ylide. They succeeded in taking advantage of both the precursors by hybridizing the coupling between the two. In 2018, Maulide and co-workers designed a new reaction between two nucleophiles: carbene precursor sulfoxonium ylide and diazo compounds, and explored the difference between




Scheme 75 Mechanism for redox neutral annulation of sulfoxonium ylides with alkynes.

their reactivity (Scheme 76).[140] The cross olefination reaction occurred with high selectivity by using a Ru catalyst, delivering products with *Z*-selectivity (**65a–j**).

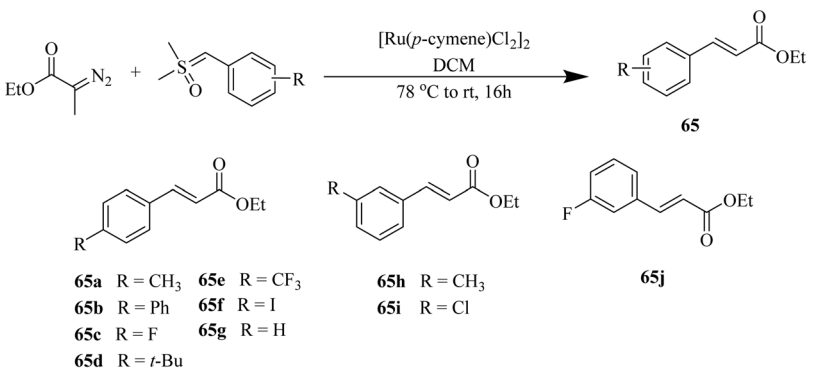
Recently, in 2019, Prabhu and his co-workers also carried out the synthesis of furanone fused 1-naphthols (**66a–m**) by using a domino C–H activation strategy under the assistance of sulfoxonium ylide as a traceless directing group (Scheme 77).[141] It involved the reaction of sulfoxonium ylides with 4-hydroxy-2-alkanoate to form heteroaromatic polycyclic compounds. The reaction proceeded through regioselective C–H activation and subsequently followed the annulation and lactonization reactions. The application of this methodology was supported by the synthesis of bromo-lactones, as the products obtained were analogues of fimbricalyx lactone A, by a step economical cascade reaction.

Aïssa and co-workers developed another protocol using sulfoxonium ylide as a traceless directing group (Scheme 78).[142] They reported intramolecular cyclization of α-carbonyl sulfoxonium ylides mounted on aryls only under basic conditions, maintained by HFIP. To demonstrate the broad applicability of this method, it was applied for the cyclization of α-carbonyl sulfoxonium ylides installed on heteroaryls such as indole, furan and pyrrole. When extrapolated to indole derivatives, intramolecular cyclization proceeded smoothly, giving almost a 50 percent yield of the cyclized product and a 31 percent yield of an intermediate which eventually gets converted into the product by using $K_2CO_3$ in HFIP at 60 °C. However, the application of this catalytic methodology to benzofuran gave the product in excellent yield with high selectivity. On the other hand, when pyrrole and *N*-methyl indoles were subjected to the same conditions, they underwent a solvolysis reaction. They then optimized the reaction with these substrates and found that using 1 mol percent of iridium catalyst resulted in the desired cyclized product (**67–k**) in good yields.

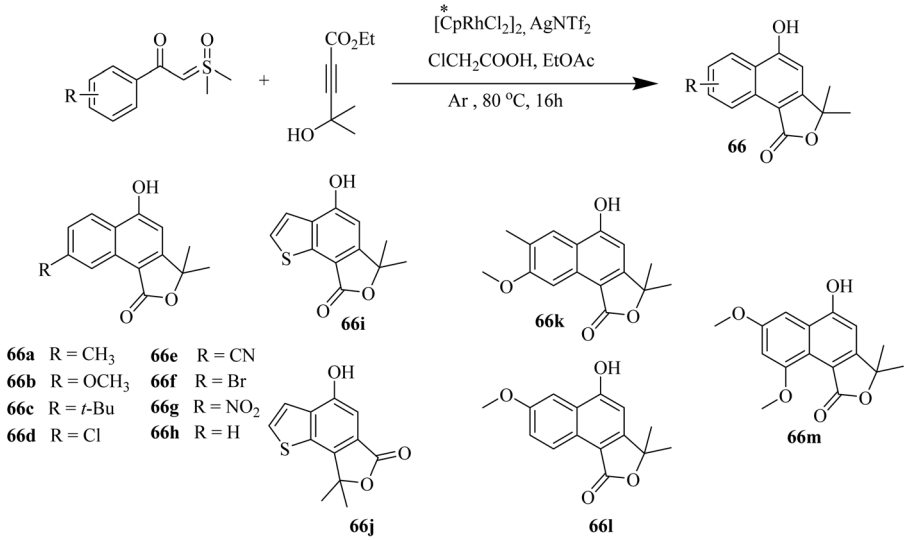
### 2.6 Si based traceless directing groups

There are several reported silicon based directing groups which have been used for halogenation, acetoxylation and other functionalization reactions.[34,143] These Si based directing groups can be easily removed due to their weak coordination with C atoms. In the majority of cases, these are removed under mild conditions but required an additional step for removal.[144,145] However, there are rare reports present in the literature wherein they exhibit a traceless character. There are only two such Si based groups which get removed autonomously in a traceless manner with a post functionalization process. Silanol and silicon tethered pyridyl diisopropyl silyl are the two groups with a traceless character.

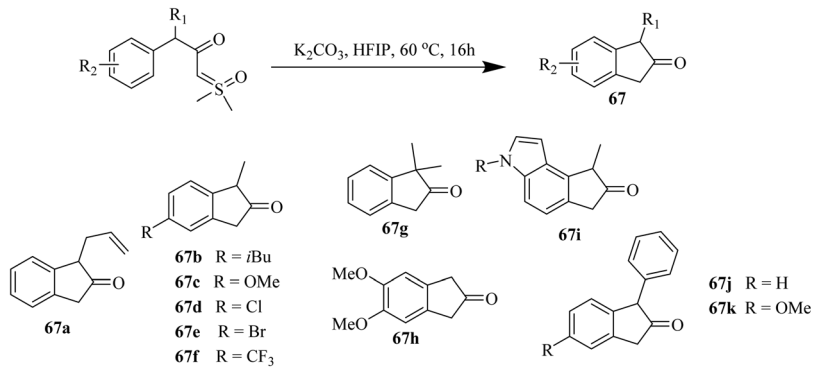
In 2011, Gevorgyan and his co-workers published work featuring Pd(II) catalyzed alkenylation of phenols using silanol as a traceless directing group. The weakly coordinating silanol group directs alkenylation of phenols selectively at the *ortho*-position (Scheme 79).[146] The reaction proceeded in a highly monoselective manner and it was found that diverse electron-withdrawing and -donating substituents were tolerated efficiently during the reaction. To illustrate the application, this methodology



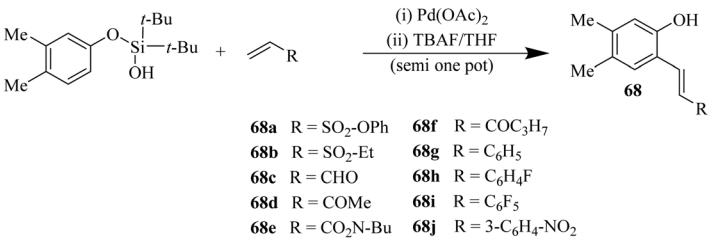

Scheme 76 Ru-Catalyzed cross olefination between carbene precursor sulfoxonium ylide and diazo compounds.




Scheme 77 Synthesis of furanone fused 1-naphthols by using a domino reaction.




Scheme 78 Intramolecular cyclisation of α-carbonyl sulfoxonium ylides.



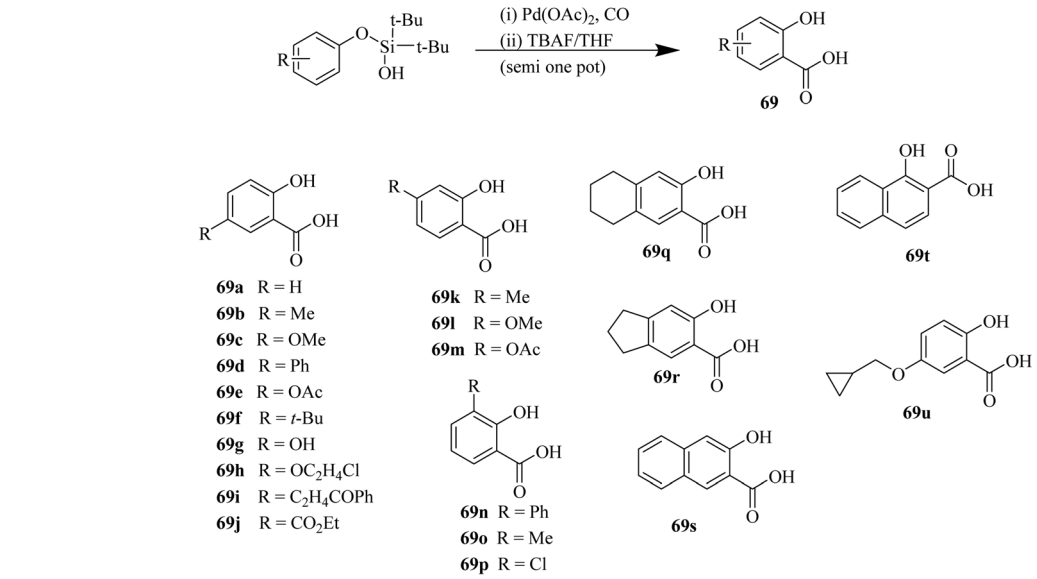

Scheme 79 Pd(II) catalyzed alkenylation of phenols using silanol as a TDG.

was applied in the synthesis of benzofuranones (**68a–j**) and alkenylated estrone derivatives.

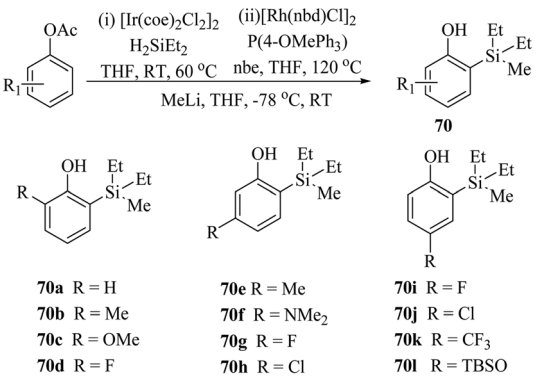
In 2015, Gevorgyan developed a novel method for palladium catalyzed synthesis of salicylic acids from phenols under the assistance of a silanol directing group (Scheme 80).[147] The silanol group efficiently and selectively directs carboxylation of phenols at the *ortho*-position and after carboxylation the silyl part departs itself from the molecule in a completely traceless manner in a one pot fashion, enabling the synthesis of salicylic acid (**69a–u**) with excellent functional group compatibility and substrate scope.

Besides Si based traceless directing groups, there are some other directing groups which have a traceless character but remained uninvestigated. There are rare reports available on such directing groups, and thus they are not discussed here. The acetal group was used for *ortho*-silylation of phenols through Rh-catalyzed nucleophilic addition to silicon, which simultaneously removed unmasked silylated phenol products




Scheme 80 Pd(II)-Catalyzed synthesis of salicylic acids form phenols.



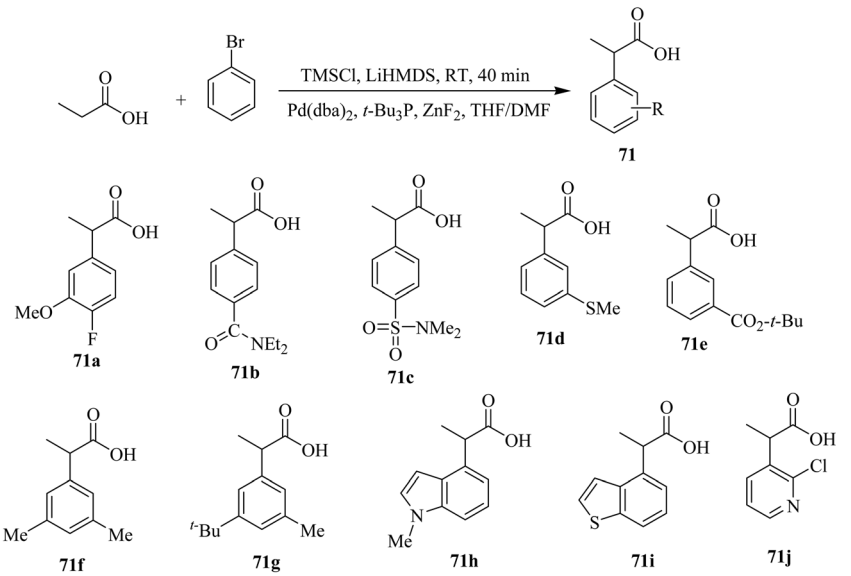

Scheme 81 Rh(III) catalyzed synthesis of dioxasilanes.

such as dioxasilanes, which have diverse applications (Scheme 81).[148] The reaction rests on two basic reactions in which firstly iridium catalyzed hydrosilylation of economically feasible and easily available phenyl acetates and then rhodium catalyzed *ortho*-silylation were performed to form dioxasilanes. This was followed by the most crucial step of nucleophilic addition. The nucleophilic addition to Si causes removal of the acetal (directing) group, thereby providing access to the desired unmasked phenol products (functionalized *ortho*-silyl phenols) (**70a–l**).

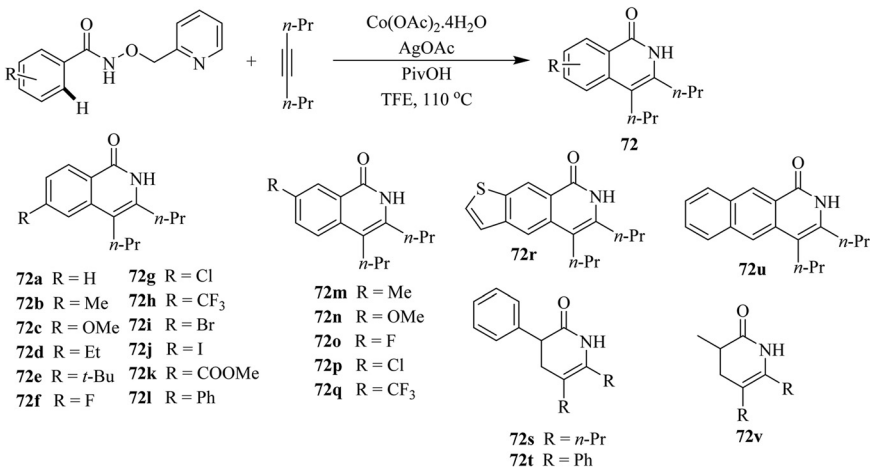
He and Hartwig have carried out α-arylation of carboxylic acids and amides by using trimethylsilyl as a directing group, which binds transiently to an acid or amide moiety and gets removed itself *in situ* after directing regioselective α-arylation. This novel attempt served as a reliable solution to longstanding challenges which did not allow the intermolecular coupling of aliphatic carboxylic acids with aryl halides. A series of reagents were used that could protect carboxylic acids and effect arylation by transiently binding to acids or amides. However, the maximum yield was obtained when trimethylsilyl chloride (TMSCl) was used as a reagent with $Pd(dba)_2$ as a catalyst. The reaction went smoothly with a variety of substituted aryl bromides and acids/amides with base sensitive functionalities such as acyl, cyano, hydroxy, nitro and alkoxycarbonyl. This methodology was found to be of high practical value as the approach was applicable for the synthesis of five commercial drugs in one step. Gram scale synthesis of a number of vital medications such as Naproxen and Flubriprofen was achieved by using this approach (Scheme 82).[149]

A novel traceless directing group 2-(hydroxymethyl)pyridine was introduced recently in 2020 (Scheme 83).[150] It assisted a novel Cp* free cobalt catalyzed approach for the synthesis of isoquinolines (**72a–v**) through a C–H activation/annulation reaction of *N*-(pyridin-2-ylmethoxy)benzamide with internal alkynes (such as diphenylacetylenes). It was observed that bemzamides substituted with electron donating groups at the *para*-position smoothly underwent the transformation, giving the desired products in excellent yields, except the *para*-methoxy group, which gave an apparently low yield. Electron-withdrawing groups such F, Cl, Br, I, $CF_3$ *etc.* also delivered the products in good yields. *meta*-Substituted substrates gave highly regioselective products and further the regioselectivity was increased with the increase in the steric hindrance of the substituent.

It is evident that in the last few decades, directing group assisted C–H functionalization has gained exceptional attention due to their remarkable potential to assist regioselective transformations with enhanced reactivity. But besides this there are a few challenges which emerged in chelation assisted C–H functionalization. One of these is the pre-functionalization and post-functionalization events and the other is the intrinsic metal coordinating properties, which may lead to metal poisoning. Moreover, there is a lack of sites required for directing group installation in the case of heteroarene. To combat the emerging issues, it has evolved in the last few years where non-




Scheme 82 Regioselective α-arylation of carboxylic acids.




Scheme 83 Cp* free cobalt catalyzed synthesis of isoquinolines.

covalent interactions such as hydrogen bonding, ion–ion and ion–dipole interactions have been used to achieve functionalization at distal positions of aliphatic and aromatic systems.[151–159] It is emerging as one of the most powerful tools to replace the directing group approach.[151,152,160–169] In recent years, there are numerous reports available in the literature particularly related to distal functionalization of olefins and acetoxylation.[170–177] It is serving as an excellent approach for functionalization of bifunctional moieties. Further, it assisted in *meta* functionalization by overriding the conventional *ortho*- and *para*-selectivity of arenes.

# 3 Conclusion and future perspectives

The emergence of traceless directing groups for C–H activations has broken the stereotype of using non-removable and removable directing groups which require additional steps for their exclusion. Their use in C–H functionalization reactions has enhanced the step and atom economy of such reactions. Moreover, it has assisted in exploring new transformations and concise synthetic alternative routes to conventional lengthy pathways. It has been also employed to carry out transformations with high regioselectivity. This review has covered various traceless directing groups such as carboxylic acids, aldehydes, *N*-oxides, nitrones, *N*-nitroso amines, amides, sulfoxonium ylides and Si tethered directing groups used for assisting transition metal catalyzed C–H functionalization reactions in the last decade and signifies how these groups assist in bringing about transformations in a highly regioselective manner and get removed in tandem, thereafter, in a one pot fashion.

Although the strategy has manifested a wide variety of advances during the last decade, it is still in its infancy since it has come into sight very recently. Only a few traceless

directing groups have been studied and explored efficiently, but there are large numbers of directing groups which need to be used to explore more access routes for different synthetic reaction pathways and to allow certain substitutions that have been challenging to perform within the existing research field. It has been evident from the existing literature that the strategy encloses in itself vast potentiality; however, only a chunk of its encompassed potential has been explored. This wealth of knowledge encourages us to expect more development in this field by either unveiling the hidden potential of some functional groups to assist in the traceless directing group relay strategy or by widening the substrate scope of existing reactions. It could also involve development of novel complementary transformations from already existing traceless directing groups. In addition, the continuing interest of research could focus on employing a wide number of structurally diverse functional groups (such as amines, oximes, carbonyl, thioether, acetal and nitro groups) in this strategy. Since they are already present in versatile natural and synthetic biological scaffolds, thereby they will not require any additional steps for installation. Therefore, continuing research is required on the development of C–H functionalization assisted by traceless directing groups to give rise to novel reactivity, synthetic routes and transformations having regio- and stereo-selectivity, and step and atom economy.

## Conflicts of interest

The authors declare no competing financial interest.

## Acknowledgements

KP and GR thank SERB, New Delhi (CRG/2018/002159) and CSIR, New Delhi [(02(0310)/17/EMR-II] for financial support.

## References

1 F. Paquin, J. Rivnay, A. Salleo, N. Stingelin and C. Silva, *J. Mater. Chem. C*, 2015, **3**, 10715–10722.
2 F. Roudesly, J. Oble and G. Poli, *J. Mol. Catal. A: Chem.*, 2017, **426**, 275–296.
3 B. N. Patil, J. J. Lade, A. S. Karpe, B. Pownthurai, K. S. Vadagaonkar, V. Mohanasrinivasan and A. C. Chaskar, *Tetrahedron Lett.*, 2019, **60**, 891–894.
4 I. A. I. Mkhalid, J. H. Barnard, T. B. Marder, J. M. Murphy and J. F. Hartwig, *Chem. Rev.*, 2010, **110**, 890–931.
5 C. Jia, T. Kitamura and Y. Fujiwara, *Org. Lett.*, 2010, **32**, 2927–2930.
6 R. Giri, B. F. Shi, K. M. Engle, N. Maugel and J. Q. Yu, *Chem. Soc. Rev.*, 2009, **38**, 3242–3272.
7 X. Chen, K. M. Engle, D. H. Wang and Y. Jin-Quan, *Angew. Chem., Int. Ed.*, 2009, **48**, 5094–5115.
8 L. Ackermann, R. Vicente and A. R. Kapdi, *Angew. Chem., Int. Ed.*, 2009, **48**, 9792–9826.
9 D. J. Abrams, P. A. Provencher and E. J. Sorensen, *Chem. Soc. Rev.*, 2018, **47**, 8925–8967.
10 Y.-L. Yun, J. Yang, Y.-H. Miao, J. Sun and X.-J. Wang, *J. Saudi Chem. Soc.*, 2020, **24**, 151–185.
11 M. R. Yadav, R. K. Rit, M. Shankar and A. K. Sahoo, *Asian J. Org. Chem.*, 2015, **4**, 846–864.
12 C. Sambiagio, D. Schönbauer, R. Blieck, T. Dao-Huy, G. Pototschnig, P. Schaaf, T. Wiesinger, M. F. Zia, J. Wencel-Delord, T. Besset, B. U. W. Maes and M. Schnürch, *Chem. Soc. Rev.*, 2018, **47**, 6603–6743.
13 M. Font, J. M. Quibell, G. J. P. Perry and I. Larrosa, *Chem. Commun.*, 2017, **53**, 5584–5597.
14 C. Kuai, L. Wang, B. Li, Z. Yang and X. Cui, *Org. Lett.*, 2017, **19**, 2102–2105.
15 S. Rej, Y. Ano and N. Chatani, *Chem. Rev.*, 2020, **120**, 1788–1887.
16 R. Jayarajan, H. B. Chandrashekar, A. K. Dalvi and D. Maiti, *Chem. – Eur. J.*, 2020, **56**, 7281–7284.
17 S. Agasti, A. Dey and D. Maiti, *Chem. Commun.*, 2017, **53**, 6544–6556.
18 S. Bag, M. Petzold, A. Sur, S. Bhowmick, D. B. Werz and D. Maiti, *Chem. – Eur. J.*, 2019, **25**, 9433–9437.
19 S. Bag, K. Surya, A. Mondal, R. Jayarajan, U. Dutta, S. Porey, R. B. Sunoj and D. Maiti, *J. Am. Chem. Soc.*, 2020, **142**, 12453–12466.
20 A. Maji, S. Guin, S. Feng, A. Dahiya, V. K. Singh, P. Liu and D. Maiti, *Angew. Chem., Int. Ed.*, 2017, **56**, 14903–14907.
21 E. Casali, P. Kalra, M. Brochetta, T. Borsari, A. Gandini, T. Patra, G. Zanoni and D. Maiti, *Chem. Commun.*, 2020, **26**, 11426–11430.
22 K. Seth, M. Bera, M. Brochetta, S. Agasti, A. Das, A. Gandini, A. Porta, G. Zanoni and D. Maiti, *ACS Catal.*, 2017, **7**, 7732–7736.
23 S. Agasti, B. Mondal, T. K. Achar, S. K. Sinha, A. Sarala Suseelan, K. J. Szabo, F. Schoenebeck and D. Maiti, *ACS Catal.*, 2019, **9**, 9606–9613.
24 T. K. Achar, K. Ramakrishna, T. Pal, S. Porey, P. Dolui, J. P. Biswas and D. Maiti, *Chem. – Eur. J.*, 2018, **24**, 17906–17910.
25 S. Porey, X. Zhang, S. Bhowmick, V. Kumar Singh, S. Guin, R. S. Paton and D. Maiti, *J. Am. Chem. Soc.*, 2020, **142**, 3762–3774.
26 K. Ramakrishna, J. P. Biswas, S. Jana, T. K. Achar, S. Porey and D. Maiti, *Angew. Chem., Int. Ed.*, 2019, **131**, 13946–13950.
27 A. Maji, A. Dahiya, G. Lu, T. Bhattacharya, M. Brochetta, G. Zanoni, P. Liu and D. Maiti, *Nat. Commun.*, 2018, 3582–3592.
28 Z. Wu, N. Fatuzzo and G. Dong, *J. Am. Chem. Soc.*, 2020, **142**, 2715–2720.
29 Z. Chen, B. Wang, J. Zhang, W. Yu, Z. Liu and Y. Zhang, *Org. Chem. Front.*, 2015, **2**, 1107–1295.
30 G. Rousseau and B. Breit, *Angew. Chem., Int. Ed.*, 2011, **50**, 2450–2494.
31 F. Zhang and D. R. Spring, *Chem. Soc. Rev.*, 2014, **43**, 6906–6919.
32 K. Gao, *Lect. Notes Comput. Sci. Eng.*, 2008, **5178**, 306–312.
33 S. J. Pastine, D. V. Gribkov and D. Sames, *J. Am. Chem. Soc.*, 2006, **128**, 14220–14221.
34 N. Chernyak, A. S. Dudnik, C. Huang and V. Gevorgyan, *J. Am. Chem. Soc.*, 2010, **132**, 8270–8272.
35 C. E. Houlden, M. Hutchby, C. D. Bailey, J. G. Ford, S. N. G. Tyler, M. R. Gagné, G. C. Lloyd-Jones and K. I. Booker-Milburn, *Angew. Chem., Int. Ed.*, 2009, **48**, 1830–1833.
36 H. Ihara and M. Suginome, *J. Am. Chem. Soc.*, 2009, **131**, 7502–7503.
37 Y. F. Zhang, H. W. Zhao, H. Wang, J. B. Wei and Z. J. Shi, *Angew. Chem., Int. Ed.*, 2015, **54**, 13686–13690.
38 F.-L. Zhang, K. Hong, T.-J. Li, H. Park and J.-Q. Yu, *Science*, 2016, **351**, 252–256.
39 Y. Wu, Y. Q. Chen, T. Liu, M. D. Eastgate and J. Q. Yu, *J. Am. Chem. Soc.*, 2016, **138**, 14554–14557.
40 X. Wang, S. Song and N. Jiao, *Chin. J. Chem.*, 2018, **36**, 213–216.
41 P. Gandeepan and L. Ackermann, *Chemistry*, 2018, **4**, 199–222.
42 F. Ma, M. Lei and L. Hu, *Org. Lett.*, 2016, **18**, 2708–2711.
43 Y. Liu and H. Ge, *Nat. Chem.*, 2017, **9**, 26–32.
44 T. Bhattacharya, S. Pimparkar and D. Maiti, *RSC Adv.*, 2018, **8**, 19456–19464.
45 Q. Zhao, T. Poisson, X. Pannecoucke and T. Besset, *Synthesis*, 2017, 4808–4826.
46 L. J. Oxtoby, Z. Q. Li, V. T. Tran, T. G. Erbay, R. Deng, P. Liu and K. M. Engle, *Angew. Chem., Int. Ed.*, 2020, **59**, 8885–8890.
47 H. Sun, N. Guimond and Y. Huang, *Org. Biomol. Chem.*, 2016, **14**, 8389–8397.
48 Q. Zhao, T. Poisson, X. Pannecoucke and T. Besset, *Synthesis*, 2017, 4808–4826.
49 A. Maehara, H. Tsurugi, T. Satoh and M. Miura, *Org. Lett.*, 2008, **10**, 1159–1162.
50 T. Patra and D. Maiti, *Chem. – Eur. J.*, 2017, **23**, 7382–7401.
51 H. A. Chiong, Q. Pham and O. Daugulis, *J. Am. Chem. Soc.*, 2007, **129**, 9879–9884.
52 L. J. Goossen, C. Linder, N. Rodrı, P. P. Lange and A. Fromm, *Chem. Commun.*, 2009, 7173–7175.
53 L. J. Goossen, W. R. Thiel, N. Rodríguez, C. Linder and B. Melzer, *Adv. Synth. Catal.*, 2007, **349**, 2241–2246.

54 C. Wang, I. Piel and F. Glorius, *J. Am. Chem. Soc.*, 2009, **131**, 4194–4195.
55 C. Wang, S. Rakshit and F. Glorius, *J. Am. Chem. Soc.*, 2010, **132**, 14006–14008.
56 S. Mochida, K. Hirano, T. Satoh and M. Miura, *Org. Lett.*, 2010, **12**, 5776–5779.
57 J. Cornella, M. Righi and I. Larrosa, *Angew. Chem., Int. Ed.*, 2011, **50**, 9429–9432.
58 S. Mochida, K. Hirano, T. Satoh and M. Miura, *J. Org. Chem.*, 2011, **76**, 3024–3033.
59 C. Arroniz, A. Ironmonger, G. Rassias and I. Larrosa, *Org. Lett.*, 2013, **15**, 2008–2011.
60 S. Bhadra, W. I. Dzik and L. J. Goossen, *Angew. Chem., Int. Ed.*, 2013, **52**, 2959–2962.
61 J. Luo, S. Preciado and I. Larrosa, *J. Am. Chem. Soc.*, 2014, **136**, 4109–4112.
62 Y. Quan and Z. Xie, *J. Am. Chem. Soc.*, 2014, **136**, 15513–15516.
63 S. Agasti, U. Sharma, T. Naveen and D. Maiti, *Chem. Commun.*, 2015, **51**, 5375–5378.
64 S. Agasti, S. Maity, K. J. Szabo and D. Maiti, *Adv. Synth. Catal.*, 2015, **357**, 2331–2338.
65 Y. Zhang, H. Zhao, M. Zhang and W. Su, *Angew. Chem., Int. Ed.*, 2015, **54**, 3817–3821.
66 X. Qin, D. Sun, Q. You, Y. Cheng, J. Lan and J. You, *Org. Lett.*, 2015, **17**, 1762–1765.
67 S. Pan, B. Zhou, Y. Zhang, C. Shao and G. Shi, *Synlett*, 2016, 277–281.
68 J. Luo, S. Preciado and I. Larrosa, *Chem. Commun.*, 2015, **51**, 3127–3130.
69 D. Lee and S. Chang, *Chem. – Eur. J.*, 2015, **21**, 5364–5368.
70 X. Y. Shi, K. Y. Liu, J. Fan, X. F. Dong, J. F. Wei and C. J. Li, *Chem. – Eur. J.*, 2015, **21**, 1900–1903.
71 R. Mei, C. Zhu and L. Ackermann, *Chem. Commun.*, 2016, **52**, 13171–13174.
72 J. Zhang, R. Shrestha, J. F. Hartwig and P. Zhao, *Nat. Chem.*, 2016, **8**, 1144–1151.
73 M. Simonetti and I. Larrosa, *Nat. Chem.*, 2016, **8**, 1086–1088.
74 L. Huang and D. J. Weix, *Org. Lett.*, 2016, **18**, 5432–5435.
75 S. Agasti, A. Dey and D. Maiti, *Chem. Commun.*, 2016, **52**, 12191–12194.
76 K. Kim, D. Vasu, H. Im and S. Hong, *Angew. Chem., Int. Ed.*, 2016, **55**, 8652–8655.
77 A. J. S. Johnston, K. B. Ling, D. Sale, N. Lebrasseur and I. Larrosa, *Org. Lett.*, 2016, **18**, 6094–6097.
78 K. R. Bettadapur, V. Lanke and K. R. Prabhu, *Chem. Commun.*, 2017, **53**, 6251–6254.
79 A. Mandal, H. Sahoo, S. Dana and M. Baidya, *Org. Lett.*, 2017, **19**, 4138–4141.
80 N. Y. P. Kumar, T. Rogge, S. R. Yetra, A. Bechtoldt, E. Clot and L. Ackermann, *Chem. – Eur. J.*, 2017, **23**, 17449–17453.
81 A. Biafora, B. A. Khan, J. Bahri, J. M. Hewer and L. J. Goossen, *Org. Lett.*, 2017, **19**, 1232–1235.
82 J. L. Yu, S. Q. Zhang and X. Hong, *J. Am. Chem. Soc.*, 2017, **139**, 7224–7243.
83 S. Yang, F. Wang, Y. Wu, W. Hua and F. Zhang, *Org. Lett.*, 2018, **20**, 1491–1495.
84 M. Font, A. R. A. Spencer and I. Larrosa, *Chem. Sci.*, 2018, **9**, 7133–7137.
85 Z. Fu, Y. Jiang, S. Wang, Y. Song, S. Guo and H. Cai, *Org. Lett.*, 2019, **21**, 3003–3007.
86 M. S. Sherikar and K. R. Prabhu, *Org. Lett.*, 2019, **21**, 4525–4530.
87 A. R. A. Spencer, R. Korde, M. Font and I. Larrosa, *Chem. Sci.*, 2020, **11**, 4204–4208.
88 X. Liu, X. Li, H. Liu, Q. Guo, J. Lan, R. Wang and J. You, *Org. Lett.*, 2015, **17**, 2936–2939.
89 J. Luo, S. Preciado, S. O. Araromi and I. Larrosa, *Chem. – Asian J.*, 2016, **11**, 347–350.
90 K. Srinivas, S. K. Siddiqui, J. K. Mudaliar and C. V. Ramana, *J. Org. Chem.*, 2019, **84**, 5056–5066.
91 S. Q. Chen, X. R. Li, C. J. Li, J. Fan, Z. W. Liu and X. Y. Shi, *Org. Lett.*, 2020, **22**, 1259–1264.
92 X. Huang, J. Huang, C. Du, X. Zhang, F. Song and J. You, *Angew. Chem., Int. Ed.*, 2013, **52**, 12970–12974.
93 R. Sharma, R. Kumar, I. Kumar and U. Sharma, *Eur. J. Org. Chem.*, 2015, 7519–7528.
94 M. Sen, D. Kalsi and B. Sundararaju, *Chem. – Eur. J.*, 2015, **21**, 15529–15533.
95 N. Barsu, M. Sen, J. R. Premkumar and B. Sundararaju, *Chem. Commun.*, 2016, **52**, 1338–1341.
96 B. Li, H. Xu, H. Wang and B. Wang, *ACS Catal.*, 2016, **6**, 3856–3862.
97 F. Cardona and A. Goti, *Angew. Chem., Int. Ed.*, 2005, **44**, 7832–7835.
98 H. Yan, H. Wang, X. Li, X. Xin, C. Wang and B. Wan, *Angew. Chem.*, 2015, **127**, 10759–10763.
99 R. B. Dateer and S. Chang, *J. Am. Chem. Soc.*, 2015, **137**, 4908–4911.
100 H. Yan, X. Li, C. Wang and B. Wan, *Org. Chem. Front.*, 2017, **4**, 1833–1838.
101 Z. Qi, M. Wang and X. Li, *Org. Lett.*, 2013, **15**, 5440–5443.
102 F. Xie, S. Yu, Z. Qi and X. Li, *Angew. Chem., Int. Ed.*, 2016, **55**, 15351–15355.
103 Q. Wang, Y. Xu, X. Yang, Y. Li and X. Li, *Chem. Commun.*, 2017, **53**, 9640–9643.
104 D. Bai, Q. Jia, T. Xu, Q. Zhang, F. Wu, C. Ma, B. Liu, J. Chang and X. Li, *J. Org. Chem.*, 2017, **82**, 9877–9884.
105 X. Guo, J. Han, Y. Liu, M. Qin, X. Zhang and B. Chen, *J. Org. Chem.*, 2017, **82**, 11505–11511.
106 H. Deng, H. Li, W. Zhang and L. Wang, *Chem. Commun.*, 2017, **53**, 10322–10325.
107 B. C. Challis and J. A. Challis, *Supplement F: The Chemisrty of Amino, Nitroso and Nitro Compounds and their Derivatives*, vol. 2, 2010.
108 J. Lee, L. Chen, A. H. West and G. B. Richter-Addo, *Chem. Rev.*, 2002, **102**, 1019–1066.
109 B. Liu, Y. Fan, Y. Gao, C. Sun, C. Xu and J. Zhu, *J. Am. Chem. Soc.*, 2013, **135**, 468–473.
110 C. Wang and Y. Huang, *Org. Lett.*, 2013, **15**, 5294–5297.
111 Y. Wu, L. J. Feng, X. Lu, F. Y. Kwong and H. B. Luo, *Chem. Commun.*, 2014, **50**, 15352–15354.
112 J. Wang, M. Wang, K. Chen, S. Zha, C. Song and J. Zhu, *Org. Lett.*, 2016, **18**, 1178–1181.
113 Y. Liang and N. Jiao, *Angew. Chem., Int. Ed.*, 2016, **55**, 4035–4039.
114 X. Song, C. Gao, B. Li, X. Zhang and X. Fan, *J. Org. Chem.*, 2018, **83**, 8509–8521.
115 X. Hu, X. Chen, Y. Shao, H. Xie, Y. Deng, Z. Ke, H. Jiang and W. Zeng, *ACS Catal.*, 2018, **8**, 1308–1312.
116 Y. Liu, Y. Tian, K. Su, P. Wang, X. Guo and B. Chen, *Org. Chem. Front.*, 2019, **6**, 3973–3977.
117 L. Liu, J. Li, W. Dai, F. Gao, K. Chen, Y. Zhou and H. Liu, *Molecules*, 2020, **4**, 1–15.
118 D. Zhao, Z. Shi and F. Glorius, *Angew. Chem., Int. Ed.*, 2013, **52**, 12426–12429.
119 K. Muralirajan and C. H. Cheng, *Adv. Synth. Catal.*, 2014, **356**, 1571–1576.
120 L. Zheng and R. Hua, *Chem. – Eur. J.*, 2014, **20**, 2352–2356.
121 S. Zhou, M. Wang, L. Wang, K. Chen, J. Wang, C. Song and J. Zhu, *Org. Lett.*, 2016, **18**, 5632–5635.
122 S. Zhou, J. Wang, F. Zhang, C. Song and J. Zhu, *Org. Lett.*, 2016, **18**, 2427–2430.
123 S. Zhou, J. Wang, P. Chen, K. Chen and J. Zhu, *Chem. – Eur. J.*, 2016, **22**, 14508–14512.
124 A. Lerchen, S. Vásquez-Céspedes and F. Glorius, *Angew. Chem., Int. Ed.*, 2016, **55**, 3208–3211.
125 J. W. Park, B. Kang and V. M. Dong, *Angew. Chem., Int. Ed.*, 2018, **57**, 13598–13602.
126 V. G. Zaitsev, D. Shabashov and O. Daugulis, *J. Am. Chem. Soc.*, 2005, **127**, 13154–13155.
127 F. Ling, C. Ai, Y. Lv and W. Zhong, *Adv. Synth. Catal.*, 2017, **359**, 3707–3712.
128 S. Yu, N. Lv, Z. Liu and Y. Zhang, *Adv. Synth. Catal.*, 2020, **362**, 118–125.
129 Y. Wang, B. Li and B. Wang, *Org. Lett.*, 2020, **22**, 83–87.
130 M. Shankar, K. Ghosh, K. Mukherjee, R. K. Rit and A. K. Sahoo, *Org. Lett.*, 2016, **18**, 6416–6419.
131 M. Shankar, T. Guntreddi, E. Ramesh and A. K. Sahoo, *Org. Lett.*, 2017, **19**, 5665–5668.
132 M. Barday, C. Janot, N. R. Halcovitch, J. Muir and C. Aïssa, *Angew. Chem., Int. Ed.*, 2017, **56**, 13117–13121.
133 Y. Xu, X. Yang, X. Zhou, L. Kong and X. Li, *Org. Lett.*, 2017, **19**, 4307–4310.
134 Z. Liu, B. Liu, X. F. Zhao, Y. B. Wu and X. Bi, *Eur. J. Org. Chem.*, 2017, 928–932.

135 H. Yamamoto and Z. Li, *Synfacts*, 2011, 0638.
136 I. Rivilla, W. M. C. Sameera, E. Alvarez, M. M. Díaz-Requejo, F. Maseras and P. J. Pérez, *Dalton Trans.*, 2013, **42**, 4132–4138.
137 D. Zhang, G. Xu, D. Ding, C. Zhu, J. Li and J. Sun, *Angew. Chem., Int. Ed.*, 2014, **53**, 11070–11074.
138 C. Zhu, G. Xu, D. Ding, L. Qiu and J. Sun, *Org. Lett.*, 2015, **17**, 4244–4247.
139 R. Oost, J. D. Neuhaus, J. Merad and N. Maulide, *Top. Curr. Chem.*, 2017, **376**, 415–462.
140 J. D. Neuhaus, A. Bauer, A. Pinto and N. Maulide, *Angew. Chem., Int. Ed.*, 2018, **57**, 16215–16218.
141 V. Hanchate, A. Kumar and K. R. Prabhu, *Org. Lett.*, 2019, **21**, 8424–8428.
142 D. Clare, B. C. Dobson, P. A. Inglesby and C. Aïssa, *Angew. Chem., Int. Ed.*, 2019, **58**, 16198–16202.
143 A. S. Dudnik, N. Chernyak, C. Huang and V. Gevorgyan, *Angew. Chem., Int. Ed.*, 2010, **49**, 8729–8732.
144 K. Itami, K. Mitsudo, T. Kamei, T. Koike, T. Nokami and J. I. Yoshida, *J. Am. Chem. Soc.*, 2000, **122**, 12013–12014.
145 K. Itami and J. I. Yoshida, *Synlett*, 2006, 157–180.
146 C. Huang, B. Chattopadhyay and V. Gevorgyan, *J. Am. Chem. Soc.*, 2011, **133**, 12406–12409.
147 D. Sarkar and V. Gevorgyan, *Chem. – Eur. J.*, 2016, **22**, 11201–11204.
148 Y. Hua, P. Asgari, T. Avullala and J. Jeon, *J. Am. Chem. Soc.*, 2016, **138**, 7982–7991.
149 Z. T. He and J. F. Hartwig, *J. Am. Chem. Soc.*, 2019, **141**, 11749–11753.
150 M. Liu, J. L. Niu, D. Yang and M. P. Song, *J. Org. Chem.*, 2020, **85**, 4067–4078.
151 T. Patra, R. Watile, S. Agasti, T. Naveen and D. Maiti, *Chem. Commun.*, 2016, **52**, 2027–2030.
152 M. Bera, A. Maji, S. K. Sahoo and D. Maiti, *Angew. Chem., Int. Ed.*, 2015, **54**, 8515–8519.
153 S. Bag, R. Jayarajan, R. Mondal and D. Maiti, *Angew. Chem., Int. Ed.*, 2017, **56**, 3182–3186.
154 M. Bera, S. Agasti, R. Chowdhury, R. Mondal, D. Pal and D. Maiti, *Angew. Chem., Int. Ed.*, 2017, **56**, 5272–5276.
155 S. Bag, K. Surya, A. Mondal, R. Jayarajan, U. Dutta, S. Porey, R. B. Sunoj and D. Maiti, *J. Am. Chem. Soc.*, 2020, **142**, 12453–12466.
156 M. Brochetta, T. Borsari, S. Bag, S. Jana, S. Maiti, A. Porta, D. B. Werz, G. Zanoni and D. Maiti, *Chem. – Eur. J.*, 2019, **25**, 10323–10327.
157 M. Bera, A. Modak, T. Patra, A. Maji and D. Maiti, *Org. Lett.*, 2014, **16**, 5760–5763.
158 T. K. Achar, X. Zhang, R. Mondal, M. S. Shanavas, S. Maiti, S. Maity, N. Pal, R. S. Paton and D. Maiti, *Angew. Chem., Int. Ed.*, 2019, **58**, 10353–10360.
159 T. K. Achar, J. P. Biswas, S. Porey, T. Pal, K. Ramakrishna, S. Maiti and D. Maiti, *J. Org. Chem.*, 2019, **84**, 8315–8321.
160 C. J. Collett, R. S. Massey, J. E. Taylor, O. R. Maguire, A. M. C. O'Donoghue and A. D. Smith, *Angew. Chem., Int. Ed.*, 2015, **54**, 6887–6892.
161 U. Dutta, S. Maiti, S. Pimparkar, S. Maiti, L. R. Gahan, E. H. Krenske, D. W. Lupton and D. Maiti, *Chem. Sci.*, 2019, **10**, 7426–7432.
162 T. Patra, S. Bag, R. Kancherla, A. Mondal, A. Dey, S. Pimparkar, S. Agasti, A. Modak and D. Maiti, *Angew. Chem., Int. Ed.*, 2016, **55**, 7751–7755.
163 N. Thrimurtulu, A. Dey, A. Singh, K. Pal, D. Maiti and C. M. R. Volla, *Adv. Synth. Catal.*, 2019, **361**, 1441–1446.
164 A. Modak, A. Mondal, R. Watile, S. Mukherjee and D. Maiti, *Chem. Commun.*, 2016, **52**, 13916–13919.
165 S. Maity, P. Dolui, R. Kancherla and D. Maiti, *Chem. Sci.*, 2017, **8**, 5181–5185.
166 S. Maity, E. Hoque, U. Dhawa and D. Maiti, *Chem. Commun.*, 2016, **52**, 14003–14006.
167 S. Bag and D. Maiti, *Synthesis*, 2016, 804–815.
168 A. Deb and D. Maiti, *Eur. J. Org. Chem.*, 2017, 1239–1252.
169 A. Deb, A. Hazra, Q. Peng, R. S. Paton and D. Maiti, *J. Am. Chem. Soc.*, 2017, **139**, 5760–5775.
170 S. K. Sinha, G. Zanoni and D. Maiti, *Asian J. Org. Chem.*, 2018, **7**, 1178–1192.
171 A. Maji, B. Bhaskararao, S. Singha, R. B. Sunoj and D. Maiti, *Chem. Sci.*, 2016, **7**, 3147–3153.
172 R. Jayarajan, J. Das, S. Bag, R. Chowdhury and D. Maiti, *Angew. Chem., Int. Ed.*, 2018, **57**, 7659–7663.
173 U. Dutta, A. Modak, B. Bhaskararao, M. Bera, S. Bag, A. Mondal, D. W. Lupton, R. B. Sunoj and D. Maiti, *ACS Catal.*, 2017, **7**, 3162–3168.
174 A. Dey, S. K. Sinha, T. K. Achar and D. Maiti, *Angew. Chem., Int. Ed.*, 2019, **58**, 10820–10843.
175 A. Dey, S. Maity and D. Maiti, *Chem. Commun.*, 2016, **52**, 12398–12414.
176 A. Dey, S. Agasti and D. Maiti, *Org. Biomol. Chem.*, 2016, **14**, 5440–5453.
177 S. Bag, T. Patra, A. Modak, A. Deb, S. Maity, U. Dutta, A. Dey, R. Kancherla, A. Maji, A. Hazra, M. Bera and D. Maiti, *J. Am. Chem. Soc.*, 2015, **137**, 11888–11891.