Transient directing groups in metal-organic cooperative catalysis

DOI: 10.1002/chem.202101598

Review

Received: 05.Mai 2021

Accepted Article published: 19.Juli 2021

# Transient Directing Groups in Metal--Organic Cooperative Catalysis

Clément Jacob,*[a,b] Prof. Bert^^U.^^W. Maes0000-0003-0431-7606,[b] Prof. Gwilherm Evano0000-0002-2939-4766*[a]

[a] <orgDiv/>Laboratoire de Chimie Organique, <orgDiv/>Service de Chimie et Physico-Chimie Organiques
<orgName/>Université libre de Bruxelles (ULB)
<street/>Avenue F.D. Roosevelt 50, CP160/06, <postCode/>1050 <city/>Brussels (<country/>Belgium)
E-mail: Clement.Jacob@ulb.be
E-mail: Gwilherm.Evano@ulb.be

[b] <orgDiv/>Organic Synthesis Division, <orgDiv/>Department of Chemistry
<orgName/>University of Antwerp
<street/>Groenenborgerlaan 171, <postCode/>2020 <city/>Antwerp (<country/>Belgium)

**Strategic functionalization**: The direct functionalization of C<C->H bonds is among the most important transformations in organic synthesis, but its efficiency depends on its selectivity, which can be controlled by the innate reactivity of the substrate or a directing group. While this last strategy has turned out to be efficient, the directing groups need to be installed before and cleaved after the transformation. These two undesired synthetic operations can be avoided by using the transient directing group strategy that is comprehensively overviewed in this review article.

The direct functionalization of C<C->H bonds is among the most fundamental chemical transformations in organic synthesis. However, when the innate reactivity of the substrate

cannot be utilized for the functionalization of a given single C<C->H bond, this selective C<C->H bond functionalization mostly relies on the use of directing groups that allow bringing the catalyst in close proximity to the C<C->H bond to be activated and these directing groups need to be installed before and cleaved after the transformation, which involves two additional undesired synthetic operations. These additional steps dramatically reduce the overall impact and the attractiveness of C<C->H bond functionalization techniques since classical approaches based on substrate pre-functionalization are sometimes still more straightforward and appealing. During the past decade, a different approach involving both the in^^situ installation and removal of the directing group, which can then often be used in a catalytic manner, has emerged: the transient directing group strategy. In addition to its innovative character, this strategy has brought C<C->H bond functionalization to an unprecedented level of usefulness and has enabled the development of remarkably efficient processes for the direct and selective introduction of functional groups onto both aromatic and aliphatic substrates. The processes unlocked by the development of these transient directing groups will be comprehensively overviewed in this review article.

The direct functionalization of C<C->H bonds is among the most important transformations in organic synthesis, but its efficiency depends on its selectivity that can be controlled by the innate reactivity of the substrate or a directing group. We review and discuss in a comprehensive manner C<C->H functionalization processes based on the transient directing group strategy. For more information, see the Review by Gwilherm Evano et^^al. on page <?><?>.

C<C->H functionalization
cooperative catalysis
organometallic catalysis
synergistic metal catalysis
transient directing groups

Review: Transient Directing Groups in Metal-Organic Cooperative Catalysis (Evano et^^al.)

@ULBruxelles @UAntwerpen

## 1. Introduction

Over the last decades, transition-metal-catalyzed cross-coupling reactions have emerged as remarkably efficient synthetic tools for the construction of carbon-carbon and carbon-heteroatom bonds, which notably led Heck, Negishi and Suzuki to be awarded the 2010 Nobel Prize in chemistry.[1,2] While such processes have revolutionized synthetic chemistry, they however require the pre-functionalization of the substrate, mostly by halogenation or metalation, to unlock reactivity towards transition-metal catalysts. This generates unwanted waste and requires at least one additional synthetic step that can be avoided by directly activating a much more inert carbon-hydrogen bond in a selective manner in a so-called C<C->H activation process.

For the C<C->H activation and functionalization to be of any synthetic usefulness, a single C<C->H bond must be activated with high levels of selectivity. Two strategies were implemented to reach high levels of regioselectivity, the first one being based on the innate reactivity of the substrate in which a given C<C->H bond is more activated than the others and can therefore be selectively activated by a given catalyst. Though this is fixed for certain C<C->H bonds in a given molecule, altering the electronic properties of the functional groups present in the substrate by acid-base interactions or by hydrogen-bonding can alter this selectivity, offering some degree of flexibility.[3] The other and probably more general strategy is based on the use of directing groups embedded in the substrate, either acting as mono- or bidentate ligands for a transition-metal catalyst that will, upon coordination of the latter, bring the metallic center in close proximity to a specific, relatively inert, C<C->H bond to be activated and enable its selective functionalization (Scheme^^1<schr1>, a).[4] While this strategy is highly attractive, avoiding the pre-functionalization of the substrate mentioned above, the directing group moiety needs, most of the time, to be installed before and cleaved after the C<C->H bond functionalization event, therefore requiring at least two additional and unwanted synthetic transformations. Moreover, the cleavage of the directing group often turns out to be rather tricky, requiring harsh conditions, or even not possible. These additional steps

required for the introduction of the directing group therefore dramatically reduce the overall impact and the attractiveness of C<C->H bond functionalization techniques since classical approaches based on the pre-functionalization of the substrate sometimes remain more straightforward and appealing, mainly depending on the accessibility of the pre-functionalized substrate. Of course, native functional groups can also act as directing groups and, in this case, the specific drawbacks are obviously not applicable, though some degree of conformational bias in the substrate is often still required to achieve efficient processes.[5]

Over the past decade, a different approach involving both the in^^situ installation and removal of the directing group, used in catalytic or stoichiometric amounts, has emerged: the transient directing group strategy (Scheme^^1<xschr1>, b). In addition to its innovative character, this strategy has brought C<C->H bond functionalization to an unprecedented level of usefulness and has enabled the development of a series of remarkably efficient processes for the direct and selective introduction of a plethora of functional groups, in a single step, onto both aromatic and aliphatic substrates. The use of such transient species moreover enabled the development of metal<C->organic cooperative catalysis, based on their synergistic use along with transition-metals, and led to the development of highly efficient, straightforward, and selective methods for the construction of carbon-carbon as well as carbon-heteroatom bonds.

Whether using a transient or a pre-installed directing group, C<C->H bond functionalization processes often require the use of carbonate or acetate bases to promote either concerted-metalation-deprotonation (CMD) or base-assisted electrophilic substitution (BAES) processes,[6] as well as silver salts acting as halide scavengers. From a mechanistic perspective, these processes using a transient directing group would start with the in^^situ installation of the transient directing mediator followed by coordination of the transition-metal catalyst and further C<C->H activation through the processes mentioned above to usually

form a stable metallacycle. Subsequently, a functionalization event would occur with a coupling partner to afford the corresponding functionalized substrate, still bearing the transient directing group, which would eventually be cleaved in^^situ to yield the desired functionalized substrate. Obviously, controlling the directing group introduction and removal rates *versus* catalysis constitutes a big challenge.

Thus, a transient directing group (TDG) will be defined throughout this review article as a group capable of coordinating a transition-metal catalyst and further selectively bringing it towards the bond to be activated, this group being installed upon reversible binding, through covalent or non-covalent weak interactions, of the substrate with an external transient directing mediator (TDM), used either in catalytic or stoichiometric amounts. Moreover, this TDG must be cleaved in^^situ after the functionalization process, thereby restoring the original functionality of the substrate.

In this review article, C<C->H functionalization processes based on the transient directing group strategy will be overviewed and discussed in a comprehensive manner. These processes have been classified according to the nature of the transient directing group and the C<C->H bond activated (i.^e. C($sp^2$)<C->H or C($sp^3$)<C->H), the former being more important than the latter from a purely synthetic point of view. Thus, this review article covers the use of transient phosphites and phosphinites, scaffolding-ligands, imines, and carbon-dioxide-derived directing groups, as well as norbornene-mediated transformations and non-covalently attached directing groups. Noteworthy, a range of review articles of high-quality have been published recently, although often only partially covering the aspects mentioned above.[7]

Eventually, as this review article aims to focus on transient directing groups, “traceless” and “two-in-one” directing groups will not be discussed here since the directing group is either part of the substrate or the product.[8,9] Norbornene-mediated transformations

leading to the *ipso*-functionalization of starting aryl halides or leading to norbornene-containing products will also be out of the scope of this review article as either the functional group utilized to attach the transient directing group is not recovered or the directing group is still present in the product.[10] Finally, supramolecular catalysts for hydrogenation or oxidation will not be discussed either since the metal is actually not inserted into the bond to be activated.[11]

## 2. Transient Phosphite- and Phosphinite- Directed Transformations

As mentioned above, the need for straightforward, efficient, and robust processes for the direct functionalization of organic molecules is of utmost importance and the transient directing group strategy discussed in the introductory section certainly represents one of the most efficient means to this end. The early developments in this field have relied on the in^^situ installation of phosphites and phosphinites into the substrates to be functionalized, such groups having a good ability to coordinate to a range of transition-metals. Reversible binding of the reagent utilized for the installation of the transient directing group on the substrate, generally via an oxygen-phosphorus bond, moreover offers the possibility to use these reagents in a catalytic manner, further improving the efficiency and attractiveness of the overall process. These methods involving the use of transient phosphites and phosphinites for C<C->H bond functionalization, and that have been shown to be remarkably efficient for the functionalization of phenols, anilines, and alkenes, will be overviewed in the following sections, starting with phenols and aniline.

### 2.1. C($sp^2$)<C->H *ortho*-functionalization of phenols and aniline

Polysubstituted phenols are indeed common scaffolds found at the core structure of an impressive number of natural products or molecules from the pharmaceutical and agrochemical industries, as well as in polymer and material sciences. Methods for the direct

functionalization of phenols are therefore of utmost importance and while this might seem to be a trivial task, their selective functionalization, notably at their *ortho*-positions, is not as easy to perform as one might think due to problems associated with regioselectivity and competing polyfunctionalization. Over the last decades, and in an attempt to address these limitations, several processes for the directed functionalization of *ortho*-C($sp^2$)<C->H bonds in phenols have emerged using pre-installed directing groups:[4c,12] while they have been shown to be quite efficient, they however suffer from limitations inherent to this approach that requires the pre-installation of the directing group and its subsequent cleavage under harsh conditions. In this context, the use of transient directing groups is much more appealing and has been demonstrated to be remarkably efficient for the selective functionalization of phenols. Inspired by the seminal and pioneering studies of the Parshal,[13] Lewis[14,15] and Cole-Hamilton[16] groups reported between 1969 and 1986, Bedford and coworkers disclosed in 2003 a strikingly efficient process for the *ortho*-arylation of phenols and naphthol. Their strategy is based on an in^^situ reversible transphosphinitation with different phosphinites, enabling the installation of the transient directing group in a catalytic fashion, and is relying on the use of rhodium-catalysis, the most efficient rhodium complex to perform this transformation being Wilkinson's catalyst [Scheme^^2<schr2>, Eq.^^(1)].[17a] Using this synergistic bicatalytic system, they could indeed perform the *ortho*-(hetero)arylation of *ortho*-substituted phenols and naphthol with a range of aryl bromides in very good yields, aryl chlorides being much less reactive under the reaction conditions. It is important to note that using bromobenzene as the coupling partner led to lower yields due to competing extra *ortho*- and *ortho*'-arylation of the newly installed phenyl moiety, and that extra arylation of naphthol at the 8 position could not be prevented either. In addition to the catalytic system originally developed, the use of $[Rh(COD)Cl]_2$ along with commercially available hexamethylphosphorous triamide was also shown to be rather efficient for the same transformation [Scheme^^2<xschr2>, Eq.^^(2)].[17b] This alternative $P(NMe_2)_3$ co-catalyst

was also independently developed by Oi, Inoue and coworkers in 2003,[18] and has further been studied by the Ye group in 2017 with diaryliodonium triflates in place of aryl halides as arylating agents.[19] As for the reaction mechanism, it would involve an oxidative addition of the rhodium catalyst into the C<C->X bond of the starting aryl halide followed by coordination to the substrate possessing the transient directing group, initially generated by transphosphinitation with the organic catalyst, and subsequent insertion into the C<C->H bond, now in close proximity to the metallic center. Subsequent reductive elimination would both regenerate the rhodium catalyst and deliver the arylated phosphinite product, which would then undergo a final transphosphinitation with unreacted starting phenol, affording the desired *ortho*-arylated phenol. As a note, this process could recently be extended by the Takaya group, using a single one-pot procedure, to the *ortho*-borylation of phenol in a promising 57^% yield.[20]

Later on, Bedford, Caffyn and Parshar showed that the use of another commercially available reagent, namely chlorodiisopropylphosphine, was also convenient and, in combination with rhodium catalysis, efficiently catalyzed the *ortho*-arylation of phenols thanks to a transient phosphinite directing group.[21] Eventually, the Bedford group reported in 2009 the *ortho*-arylation of various protected tyrosines with Wilkinson's catalyst,[22] the corresponding phosphinite derivatives being however pre-formed in this case to enhance the reactivity as showed in previous reports.[17,21] Another elegant and especially useful application, demonstrating the usefulness of this transient phosphinite directing group strategy, has been reported in 2016 by Ye and coworkers to promote the direct *ortho*-arylation of BINOLs yielding, in a single step, diarylated BINOL derivatives, especially useful molecules in (organo)catalysis that are not trivial to prepare. The use of $[Rh(COD)Cl]_2$, $^tBu_2PCl$, additional $Ph_2$-COD diene and $Cy_3P$^<M.>^$HBF_4$ as the catalytic system was shown to smoothly promote both the mono- (when blocking the second hydroxy group as a methyl

ether) and di- *ortho*-arylation with different aryl halides, in toluene at 120^°C, in good to excellent yields (Scheme^^3<schr3>).[23]

While these processes provide an easy access to *ortho*-arylated phenols, the main limitation being the competing diarylation when starting from non *ortho*-substituted phenols, other substituents can be introduced on phenols, transiently activated as phosphinites. Indeed, while studying and characterizing rhodium(I)-phosphinite complexes, the Ellman and Bergman group reported in 2005 the use of transient phosphinite directing groups for both the inter- and intra- molecular *ortho*-alkylation of some phenols with alkenes. Using Wilkinson's catalyst along with catalytic amounts of (2,3-xylyl)diisopropylphosphinite (*i*-$Pr_2$POXy) as the transient directing mediator at 135^°C in toluene, an *ortho*-substituted phenol could be cleanly alkylated and the intramolecular version was found to be equally efficient [Scheme^^4<schr4>, Eqs.^^(1) and (2)].[24] A year later, Cole-Hamilton and coworkers elegantly reported the ethylation of phenol and cresols in excellent yields but with limited levels of selectivity [Scheme^^4<xschr4>, Eq.^^(3)] whereas the alkylation of aniline was found to be more sluggish [48^% for mono- and di- arylation; Scheme^^4<xschr4>, Eq.^^(4)].[25]

As evidenced with all examples overviewed in this section, the use of phosphites and phosphinites as transient directing groups has enabled the development of efficient and straightforward processes for the direct functionalization of phenols and aniline. They have in addition been shown to smoothly enable the hydroformylation of alkenes that will be discussed in the next section.

**2.2 Rhodium-catalyzed hydroformylation of alkenes**

The hydroformylation of alkenes indeed offers an especially straightforward entry to aldehydes from cheap and readily available alkenes from the petrochemical industry. This transformation has been extensively studied in the past and numerous well-known industrial

processes have been developed based on this reaction, notably in the fragrance industry, even though it often requires transition-metal catalysts as well as hazardous mixtures of carbon monoxide and hydrogen gas.[26] As for the direct functionalization of phenols, the transient directing group strategy has been skillfully utilized for the development of improved and versatile processes for the hydroformylation of alkenes embedded with a hydroxyl group required for the temporary attachment of the directing group. These reactions, which can also be performed with other classes of transient directing groups that will be described later on, will be reviewed in the following paragraphs.

A pioneering report on the catalytic use of phosphinites as transient directing groups in this area was reported by Breit and coworkers in 2008. Indeed, they managed to perform the hydroformylation of various homoallylic alcohols to γ-lactones resulting from a spontaneous condensation of the alcohol to the newly generated aldehyde moiety and a subsequent oxidation of the corresponding hemiacetal, in excellent yields and regioselectivity (Scheme^^5<schr5>).[27a] The best catalytic system was found to rely on the use of $Rh(CO)_2acac$ as the catalyst in combination with catalytic amounts of $Ph_2POMe$, to install the transient directing group, under 20^^bar of syngas (1^:^1 mixture of $H_2$ and CO), in THF at 40^°C with 4^^Å molecular sieves. The latter additive, which can be replaced by catalytic amounts of lithium chloride, enabled an impressive control of the regioselectivity in favor of the 6-membered rhodacycle, thus delivering the corresponding 5-membered ring hemiacetal from a favored 6-*exo*-trig intramolecular hydrometallation over its 7-*endo*-trig counterpart. The mechanism of this directed hydroformylation is believed to first involve a transphosphinitation between the substrate and the transient directing phosphinite mediator, thus installing the transient directing group that would coordinate to the rhodium catalyst and initiate the 6-*exo*-trig hydrometallation of the alkene. Subsequent insertion of carbon monoxide would then afford the phosphinite-bound aldehyde whose transphosphinitation with

unreacted substrate would close the catalytic cycle, releasing the hydroformylated γ-hydroxyaldehyde that would undergo a final cyclization to the 5-membered ring hemiacetal.

Thereafter, the Breit group skillfully transposed this process, first in 2010 to the synthesis of 6-membered ring lactones by placing an additional methylene unit in between the alkene and the alcohol in the substrate. These δ-lactones result from a 7-*exo*-trig intramolecular hydrometallation favored over the 8-*endo*-trig one [Scheme^^6<schr6>, Eq.^^(1)].[27b] In a similar vein, they next transposed their process in 2011 to secondary substituted homoallylic alcohols, a reaction that however required an increase of the amounts of both the rhodium catalyst and the starting phosphinite under a syngas pressure of 40^^bar. With these modified conditions, they could obtain a range of substituted γ-lactones in excellent yields and selectivity towards the 6-*exo*-trig intramolecular hydrometallation [Scheme^^6<xschr6>, Eq.^^(2)].[27c] Breit and coworkers eventually reported the same year, and based on the same modified conditions, the diastereoselective hydroformylation of 2,5-cyclohexadienyl-1-carbinols to 5,6-fused bicyclic cyclohexene hemiacetals and their further oxidation into the corresponding lactones in good yields and selectivity [Scheme^^6<xschr6>, Eq.^^(3)].[27d] This regio- and diastereo- selective process thus enabled the straightforward formation of a synthetically attractive *cis*-bicyclic lactone bearing a quaternary carbon center while still offering a possibility for further functionalization of the remaining olefin.

While the use of phosphites and phosphinites as transient directing groups have now proven their potential and efficiency for the design and development of straightforward processes for the functionalization of phenols and aniline as well as for the hydroformylation of alkenes, another elegant and similar strategy has emerged in the field of transient directing groups and will be further discussed in the following section.

**3. Transient Scaffolding-Ligand-Directed Transformations**

As previously mentioned, and as illustrated in the previous section, reversible covalent binding offers unprecedented levels of efficiency and selectivity for the straightforward functionalization of C<C->H bonds in various substrates. While phosphite and phosphinite transient directing groups rely on the reversible formation of an oxygen-phosphorus covalent bond, another class of transient directing group that can be temporarily installed on an alcohol and that was independently developed for the hydroformylation of olefins, is taking advantage of a reversible carbon-oxygen bond formation. Indeed, the transient character of these so-called scaffolding-ligands lies in their efficient and reversible exchange with alcohols, enabling in addition the development of traceless diastereoselective processes that phosphites and phosphinites could not promote. These processes will be thoroughly overviewed in the following section.

In 2008, Tan and coworkers reported the first examples of the catalytic use of what they named “scaffolding-ligands”. The ligand they developed, which can be synthesized in four steps, is based on an especially convenient and well-designed 2-methoxybenzoazaphosphole that can readily undergo an acid-catalyzed reversible ether exchange with various alcohols. Indeed, in the presence of only 0.1^^mol% of *para*-toluenesulfonic acid, they could observe that an equilibration occurred between the scaffolding-ligand and primary, secondary, or even tertiary alcohols, though with an equilibration constant highly depending on steric hindrance: the more hindered the alcohol, the lesser the binding to the scaffolding-ligand [Scheme^^7<schr7>, Eq.^^(1)].[28a]

Nonetheless, upon reaction with catalytic amounts of $Rh(CO)_2acac$, the scaffolding-ligand and *p*-TsOH in the presence of 3^^Å MS under 14^^bar of a $CO/H_2$ mixture in benzene at 45 to 65^°C, they could perform, in high yields and selectivity, the hydroformylation of different homoallylic alcohols under similar conditions to those

independently reported by the Breit group (see Scheme^^6<xschr6>) the same year with transient phosphinites directing groups [Scheme^^7<xschr7>, Eq.^^(2)].

Analogous to Breit and coworkers' observations, the 7-*exo*-dig hydrometallation of the alkene was highly favored over the 8-*endo*-dig one, though to a lower extent. Similarly, the so-formed hydroxyaldehydes also underwent spontaneous cyclization to the corresponding 5-membered ring hemiacetals, which were further oxidized to the corresponding lactones. Moreover, the high *anti* selectivity observed during the lactone formation was rationalized based on minimization of 1,3-allylic strain, reduced levels of diastereoselectivity obtained with (*E*)-alkenes supporting this hypothesis. The mechanism of the transformation was proposed to first involve an ether exchange between the scaffolding-ligand and the starting alcohol prior to coordination to the rhodium hydride catalyst whereupon the 7-*exo*-dig hydrometallation of the alkene moiety would occur. Further carbon monoxide insertion and decoordination would deliver the corresponding scaffolding-ligand-bound aldehyde, thus regenerating the rhodium catalyst. Subsequent ether exchange with a new molecule of substrate would then release the alcohol that would finally spontaneously undergo intramolecular condensation to the cyclic hemiacetal, thus closing the catalytic cycle.

Few years later, the regioselectivity of the insertion process could elegantly be reversed by finely tuning the nature of the scaffolding-ligand and notably the length of the tether between the anchor point and the coordinating phosphine moiety. Various optically pure substituted homoallylic alcohols could thus be converted, after an additional oxidation step, into the corresponding δ-lactones under similar reaction conditions in fair to good yields, along with high levels of regio- and diastereo- selectivity (Scheme^^8<schr8>).[28b]

Back in 2009, the Tan group could extend this exact same method to the hydroformylation of allylic sulfonamides, substrates that gave the corresponding aldehydes as the intramolecular addition is not favored in this case [Scheme^^9<schr9>, Eq.^^(1)].[28c]

Some hemiaminals resulting from the less favored 7-*endo*-dig hydrometallation and subsequent cyclization could however be observed at lower pressure, which was found optimal at 28^^bar, thus minimizing the amount of this byproduct. Later on, Tan and coworkers could perform the hydroformylation of substituted allylic alcohols, the regioselectivity being governed by the relative stability of the 6-membered metallacycle over the 7-membered one. Subsequent selective oxidation into the corresponding carboxylic acids afforded the branched regioisomers in fair to good yields and high selectivity [Scheme^^9<xschr9>, Eq.^^(2)].[28d] Utilizing the same scaffolding-ligand, linearly substituted allylic alcohols could also be subjected to the regioselective hydroformylation and further oxidation into the corresponding branched carboxylic acids in similar yields and with excellent stereospecificity, the relative configuration of the product formed starting from trisubstituted alkenes being controlled by their stereochemistry [Scheme^^9<xschr9>, Eq.^^(3)].[28e] Here again, and for both of these examples, the use of $Rh(CO)_2acac$ along with catalytic amounts of both the scaffolding-ligand and *p*-TsOH in benzene under a 3.5 to 28^^bar pressure of $CO/H_2$ at 45^°C was shown to provide the most efficient conditions.

The Tan group eventually reported a traceless asymmetric version of this process in 2010 for the hydroformylation of *para*-methoxyphenyl (PMP) protected allylic amines[28f] and further extended it to allylic anilines,[28g] though requiring some changes in the scaffolding-ligand structure by addition of a third fused cycle bearing an extra stereogenic center (Scheme^^10<schr10>). For these processes involving an equilibrium between oxygen- and nitrogen-carbon bonds, it is worth to mention that the scaffolding-ligand and the substrate must be pre-mixed before setting up the hydroformylation, so that a pre-exchange can occur. Thereby, the use of catalytic amounts of $Rh(CO)_2acac$, the scaffolding-ligand and *p*-TsOH in benzene at 35^°C under a $CO/H_2$ pressure of 3.5^^bar and subsequent sodium borohydride reduction afforded the corresponding γ-aminoalcohols in fair to good yields and enantiomeric

excesses [Scheme^^10<xschr10>, Eqs.^^(1) and (2)], the regioselectivity still easily being explained by the relative stabilities of the 6- and 7- membered metallacycles.

Despite being notably efficient for hydroformylation reactions of allylic, homoallylic and bishomoallylic alcohol and amine derivatives through regio-, diastereo-, and even enantio- selective processes, scaffolding-ligands however enable only a narrow set of transformations along with a rather poor substrate diversity, thereby showing some major limitations. While the scaffolding-ligand transient directing group strategy is based on an exchange between an ether and an alcohol or between an ether and an amine, another class of transient directing groups that has been actively developed and studied over the last decade is based on the reversible formation of an imine, a strategy that in addition enables the use of readily available reactants for the formation of the transient directing group. The emergence of this strategy, by far the most studied in the field of directed-functionalization reactions, will be overviewed in the following section.

**4. Transient Imine-Directed Transformations**

It is no surprise that imines have attracted a great deal of attention as transient directing groups since they display all the properties required. Indeed, they are easily and reversibly formed by condensation of amines and aldehydes or ketones together with attractive kinetics. Moreover, the imine moiety shows a high affinity towards transition-metals thanks to its coordinating lone pair, thus acting as an efficient ligand for organometallic catalysis. It is in addition fairly easy to design and synthesize imine precursors embedded with an additional coordinating group, the resulting imines acting as efficient transient directing groups that have been shown over the years to enable the functionalization of C<C->H, C<C->C as well as B<C->H bonds in high yields and selectivity.[7i,j,o] The use of imines as one of the most efficient transient directing groups reported to date will therefore be

extensively discussed in the following sections, starting with the direct functionalization of C($sp^2$)<C->H bonds.

### 4.1. C($sp^2$)<C->H functionalization

#### 4.1.1. C($sp^2$)<C->H bond functionalization of aldehydes

Aldehydes are the first substrates that come to one's mind when using an imine as a transient directing group. They indeed easily form imines upon reaction with amines, in a reversible manner. The use of catalytic amounts of amines as organocatalysts for the metal-catalyzed directed functionalization of aldehydes has therefore been extensively studied and many efficient processes have been reported to date based on such a strategy.

The very first example of a direct functionalization of an aldehyde's C($sp^2$)<C->H bond taking advantage of a transient imine formation has been reported by the Jun group in 1997 and was inspired by the seminal works of Suggs[29] and Rauchfuss.[30] By combining catalytic amounts of 2-amino-3-picoline transient directing mediator and Wilkinson's catalyst in toluene at 150^°C, the alkylation of both aliphatic and aromatic aldehydes with alkenes via the transient formation of corresponding imines could be efficiently performed in moderate to good yields, a transformation that enables a straightforward and direct entry to ketones directly from aldehydes (Scheme^^11<schr11>).[31a] The mechanism of this transformation was proposed to proceed first by the condensation of 2-amino-3-picoline onto the starting aldehyde to form the corresponding imine directing group. Coordination of the Wilkinson's catalyst to the pyridine moiety would next enable its insertion into the C($sp^2$)<C->H bond to deliver a stable 5-membered rhodacycle. Subsequent coordination of the alkene to the complex followed by a 1,2-migratory insertion and further reductive elimination would then afford the alkylated imine with concomitant regeneration of the rhodium catalyst. Hydrolysis

would eventually occur to deliver the desired ketone, thereby regenerating the 2-amino-3-picoline transient directing mediator.

Subsequently, the Jun group successfully extended this method to the alkylation of heteroaromatic aldehydes to the corresponding ketones in good yields, a reaction that however required the use of a stoichiometric amount of the transient directing mediator and catalytic amounts of additives such as the Schwartz's reagent or titanocene dichloride to coordinate the heteroatoms present in the substrates that inhibit the catalytic activity otherwise [Scheme^^12<schr12>, Eq.^^(1)].[31b] Conjugated esters and amides were also found to be excellent alkylating agents provided that catalytic amounts of benzoic acid were used, offering an efficient entry to β-ketoesters and amides in excellent yields [Scheme^^12<xschr12>, Eq.^^(2)].[31c] A closely related strategy was also implemented by the Breit group in 2011 through the development of a new bidentate transient directing group in^^situ generated from a 2-amino-3-picoline moiety bearing an extra diphenylphosphinomethyl group, forming a fairly stable fused 5,5-membered rhodacycle [Scheme^^12<xschr12>, Eq.^^(3)].[31d] Jun and coworkers eventually demonstrated that the reaction could also be run in the absence of solvent with microwave activation at 140^°C.[32]

Back in 1998, the Jun group could also extend their process to benzylic alcohols that are readily oxidized to the corresponding benzaldehydes by hydrogen transfer with olefins under rhodium catalysis.[33] A large excess of the alkene is therefore required since one equivalent is consumed in this oxidation and a combination of hydrated rhodium(III) chloride, triphenylphosphine and 2-amino-4-picoline, used in stoichiometric amounts, were required for the reaction to proceed efficiently (Scheme^^13<schr13>).[34a] When starting from methanol, this process could afford a straightforward and elegant entry to symmetric ketones resulting from an in^^situ generation of formaldehyde and its subsequent double transiently imine-directed alkylation.[34b] As a note, a supported catalyst, obtained by complexation of rhodium

(III) chloride hydrate with polymer-supported phosphines, was also developed for this transformation and shown to be efficient when starting from benzylic alcohols.[34c] A second generation of supported catalytic systems was also developed based on a hydrogen bond self-assembly only occurring at low temperatures, thus offering an easy recycling of the supported catalyst by simply cooling down the system after the reaction had taken place at 150^°C.[34d,e]

In an effort to further expand the range of substrates amenable to this transformation, the Jun group demonstrated that allylic alcohols, readily isomerized to the corresponding aldehydes by the rhodium catalyst, were also good reaction partners, the transient directing mediator being used in catalytic amounts in this case (Scheme^^14<schr14>).[35]

Interestingly, the Jun group highlighted in 1999 that the reaction was not restricted to aldehydes but could also be performed starting from imines due to their easy transimination with 2-amino-3-picoline. Various imines could thus be alkylated with 1-hexene using Wilkinson's catalyst, neat at 130^°C. Different ketones could also be obtained at the cost of an additional hydrolysis step [Scheme^^15<schr15>, Eq.^^(1)].[36a] Although this is a less attractive transformation due to the poorer availability of the starting materials, the feasibility of this process opened an interesting opportunity for the Jun group to further improve their alkylation of aldehydes with unactivated alkenes by taking advantage of this easy transimination. Indeed, they could show that the addition of catalytic amounts of aniline facilitated the overall process, indicating that the transimination between aniline and the alkylated imine is more facile than the direct condensation of the transient directing mediator and the substrate [Scheme^^15<xschr15>, Eq.^^(2)].[36b]

As with aldehydes, the Jun group next demonstrated that imines could be in^^situ generated by dehydrogenation of the corresponding amines prior to a domino double transimination and further alkylation to deliver, after hydrolysis, the corresponding ketones in high yields (Scheme^^16<schr16>).[36c] As a note, benzylamine was shown to be a poor

substrate for this transformation due to an extra alkylation of the phenyl ring. The mechanism is believed to start with the oxidation of the starting primary amine to generate the corresponding imine, this step requiring the use of one sacrificial equivalent of the alkene. Transimination with unreacted amine and then with 2-amino-3-picoline allows for the installation of the transient directing group, which triggers the transient imine-directed alkylation catalytic cycle to finally release the transient imine alkylated product. Further transimination with unreacted amine and additional hydrolysis in a subsequent step would eventually afford the desired ketone.

This C($sp^2$)<C->H alkylation of aldehydes and imines with alkenes can also be performed in an intramolecular fashion when starting from aldehydes bearing a remote alkene. Such an alkylative cyclization was nicely exploited by the Breit group in 2011, which designed an elegant entry to substituted indanones from 2-vinylbenzaldehydes. Indeed, when treated with $[Rh(COD)_2]BF_4$ along with catalytic amounts of 2-amino-diphenylphosphinomethyl-3-picoline as the transient directing mediator in toluene at 150^°C, such unsaturated aldehydes could undergo intramolecular alkylation of the aldehyde moiety to deliver the corresponding cyclized product in excellent yields [Scheme^^17<schr17>, Eq.^^(1)].[31d] One year later, the Douglas group reported a related cyclization to higher carbocycles by placing one or two methylene units between the alkene and the arene and/or replacing the benzene ring by a heteroatom such as a pyrrole or an indole. Using a combination of catalytic amounts of $[Rh(COE)_2Cl]_2$, triphenylphosphine and a transient directing mediator of the 2-amino-3-picoline series along with stoichiometric amounts of aniline to facilitate the transformation through transimination, various benzaldehyde, pyrrole and indole derivatives could be smoothly cyclized in moderate to good yields, exclusively in the *endo* fashion [Scheme^^17<xschr17>, Eqs.^^(2) and (3)].[37] The enantioselectivity of the process was explored by the mean of various chiral rhodium-ligands such as a chiral phosphine, a BINAP derivative, a phosphoramidite or a chiral oxazolidinone-substituted

aminopyridine transient directing mediator, however unsuccessfully, only leading to 31^% enantiomeric excess in the best case.

As a note, the Jun group explored the application of this rhodium-catalyzed transient imine-directed alkylation of aldehydes with alkenes in the polymer and material sciences in multiple different ways. Indeed, they could perform the hydroacylation of various polybutadienes[38a--c] as well as introduce and immobilize organic functional groups such as ketones onto different solid supports.[38d,e] In a follow-up report on the rhodium-catalyzed alkylation of aliphatic aldehydes with alkenes, the Jun group also identified that the former could undergo aldolization/crotonization in^^situ, providing α,β-unsaturated aldehydes that could further be converted into the reactive aldimine through conjugated addition of a primary amine and retro-Mannich type fragmentation prior to the alkylation process.[39a] α,β-Unsaturated aldehydes could of course also be used directly.[39b--d]

This peculiar reactivity could smartly be exploited when switching from alkenes to alkyne reaction partners that can be used for the alkylation of $C(sp^2)$<C->H bonds in aldehydes and imines. Indeed, alkynes could also be utilized as alkylating agents while one would have expected they could serve as alkenylation reagents. Using Wilkinson's catalyst along with cyclohexylamine reagent in the presence of catalytic amounts of 2-amino-3-picoline and aluminum chloride, various aldehydes could indeed be alkylated with a range of symmetrical alkynes to deliver, after hydrolysis, the corresponding ketones in high to excellent yields (Scheme^^18<schr18>). This peculiar reactivity is therefore based on an especially smart reaction design also featuring a retro-Mannich fragmentation.[39e,f] The mechanism is proposed to begin with the imine condensation between the starting aldehyde and 2-amino-3-picoline to trigger the transient imine-directed, rhodium-catalyzed alkenylation with the symmetrical alkyne to the corresponding conjugated imine. Conjugated addition of cyclohexylamine then yields a β-amino-imine that subsequently undergoes a retro-Mannich

fragmentation to the corresponding enamine, in equilibrium with the imine whose hydrolysis delivers the alkylated ketone and regenerates the transient directing mediator. The only drawback of this strategy is that half of the alkyne is transformed into a reactive waste that is further alkylated with the starting alkyne in a catalytic fashion.

The classical reactivity of alkynes as alkenylation, not alkylation, agents could be restored in the absence of the additional amine and aluminum trichloride: using Wilkinson's catalyst along with catalytic amounts of 2-amino-3-picoline and benzoic acid in toluene at 80^°C, α-enones could be obtained in high to excellent yields with terminal alkynes (Scheme^^19<schr19>).[40]

While the use of aminopyridines as transient directing mediators successfully led to the development of fairly efficient and straightforward processes for the α-alkylation and/or -alkenylation of aldehydes and imines, the design of other amine-based directing groups offered interesting opportunities for the design and development of efficient and innovative processes for the functionalization of aryl C($sp^2$)<C->H bonds through transient imine-directed transformations. Their development will be extensively overviewed in the following section.

#### 4.1.2. C($sp^2$)<C->H bond functionalization of arenes

Substituted arenes are found at the core of key molecules with a broad range of applications and the functionalization of arenes is therefore still an especially active and productive area of research. In this context, the direct functionalization of C($sp^2$)<C->H bonds in arenes has received a great deal of attention over the last decades and still constitutes a challenge of utmost importance.[4,7,8] For arenes whose innate reactivity cannot be used for the selective functionalization of one of their C($sp^2$)<C->H bonds or to bypass this innate reactivity, the use of directing groups is usually the best option and has been extensively studied. In most cases however, the directing group needs to be installed and cleaved --

whenever possible -- in at least two separate steps, diminishing the attractiveness and utility of the overall process. In this perspective, the transient directing strategy is especially appealing, while however limited to arenes possessing the right functional group needed to install the transient directing group. Among all possible transient directing groups that could be reversibly installed onto an arene, imines have been the most studied, which has resulted in the development of efficient and selective processes for the functionalization of C($sp^2$)<C->H bonds in benzaldehydes.[7i,j,m] While their functionalization typically relies on the use of either uncleavable directing groups or intrinsic aldehyde weak coordinating groups in the cases of *ortho*-functionalization,[4] the use of imine transient directing groups has enabled the development of a range of transformations such as arylations, alkylations, aminations, or even selenations: these will be discussed in the following sections, starting with arylation reactions.

#### 4.1.2.1. (Hetero)arylation reactions

The first example of transient imine-directed arylation of C($sp^2$)<C->H bonds in arenes, based on a simple bidentate aminoacid as the transient directing mediator alongside with a palladium(II) catalyst, has been reported in 2017 by the groups of Yu and Zhang. Among all aminoacids screened as transient directing mediators, the ones leading to the formation of an intermediate 6-membered palladacycle afforded poor yields. α-Methylalanine was shown to be the most efficient thanks to its *gem*-dimethyl substituent and the small bite angle required for the formation of a stable 5-membered chelate. Thus, reacting benzaldehydes with (hetero)aryl iodides as arylating agents in the presence of catalytic amounts of $Pd(OAc)_2$ and α-methylalanine together with stoichiometric silver trifluoroacetate to promote a Pd(II)/Pd(IV) catalytic cycle could deliver the corresponding *ortho*-(hetero) arylated benzaldehydes in moderate to high yields (Scheme^^20<schr20>).[**41**]

The development of this process paved the way for the (hetero)arylation of aromatic aldehydes and ketones using aminoacids as transient directing mediators and other reports

were quick to follow. The groups of Xu and Jin could indeed extend this process to the *ortho*-arylation of aromatic ketones relying on the use of glycine as a transient directing mediator. In this process, $Pd(PPh_3)_2Cl_2$ and $Pd(OAc)_2$ were shown to be the palladium(II) sources of choice alongside with silver(I) acetate to promote a Pd(II)/Pd(IV) catalytic cycle by iodide abstraction. In these conditions, a range of *ortho*-arylated aromatic ketones could be delivered in fair to good yields (Scheme^^21<schr21>).[42] Supported by both intra- and inter-molecular kinetic isotope effect experiments, the mechanism is believed to proceed first by the imine formation followed by coordination of the palladium catalyst to this transient imine and further C<C->H activation to generate a stable fused 5,5-membered palladabicycle. Subsequent oxidative addition into the aryl iodide coupling partner would afford the Pd(IV) intermediate, whereupon reductive elimination would occur thanks to iodide abstraction by the silver salt to deliver the transient imine product alongside with silver iodide and the palladium catalyst. Further hydrolysis of the imine moiety would eventually release both the product and the transient aminoacid directing mediator. This process was also found to be efficient, as nicely demonstrated by the Maiti and Volla groups, for the C4 arylation of indole-3-carbaldehydes. In this case, it is interesting to note that no arylation occurred at the C2 position, probably due to a competition between fused 5,5- and 5,6- membered palladacyles, thus in favor of the latter.[43]

Following these pioneering studies on the transiently directed arylations of aromatic aldehydes and ketones with aryl iodides, a range of alternative procedures and mediators have next been reported. Indeed, the groups of Lin and Wei reported that β-aminoamides such as 2-amino-*N*-isopropylacetamide acted as efficient transient directing mediators, delivering *ortho*-arylated acetophenones in moderate to excellent yields (Scheme^^22<schr22>, a).[44] To gain more insights into the mechanism, the authors performed both intra- and inter- molecular kinetic isotope effect experiments and proposed a mechanism similar to the one depicted in

Scheme^^21<xschr21>. A tridentate dipeptide, $H_2N$-Gly-Gly-OH, was also found to be operative, with diminished efficiency though (Scheme^^22<xschr22>, b).[45]

One of the main advantages of the use of aminoacids as transient directing mediators for the arylation of aromatic aldehydes and ketones is that the use of readily available homochiral aminoacids offers interesting perspectives for enantioselective processes, although restricted to some specific substrates. The first report in this area was disclosed in 2018 by the groups of Xu and Jin which developed an elegant enantioselective palladium-catalyzed (hetero)arylation of ferrocenyl ketones with (hetero)aryl iodides in the presence of L-*tert*-leucine as transient chiral mediator allowing both the transformation to occur and the enantioselectivity to be controlled. Despite moderate yields, the *ees* were shown to be excellent, although the authors did not provide a model for the enantioselectivity observed (Scheme^^22<xschr22>, c).[46] A year later, the Shi group could apply this chiral transient directing group strategy to the development of an efficient synthesis of chiral aldehyde catalysts by atroposelective C($sp^2$)<C->H naphthylation. In this process, the authors were compelled to use strained 7-oxabenzonorbornadienes as naphthyl iodides were found to be reluctant reaction partners. Biaryls bearing an aldehyde functional group could be arylated in fair yields and excellent enantioselectivity which could be rationalized by the atroposelectivity induced by the transient chiral bulky directing group: in order to reach the C<C->H bond to be activated while minimizing the steric clash between the second aryl moiety and the transient imine species, the substrate necessarily needs to adopt a specific chiral conformation (Scheme^^22<xschr22>, d).[47]

In 2018, the group of Ge showed that not only α-aminoacids, leading to fused 5,5-membered palladabicycle intermediates, but also β-aminoacids can be used as transient directing mediators for the directed arylation of (hetero)aromatic aldehydes. Indeed, in the course of their studies on the synthesis of mechanochromic materials, they reported that the

arylation of heteroaromatic aldehydes and ketones could be efficiently performed using 3-amino-3-methylbutanoic acid, leading to fused 5,6-membered palladabicycle intermediates, while glycine, alanine and α-methylalanine were not operative. Various heteroaromatic aldehydes and ketones could thus be arylated in moderate to good yields (Scheme^^22<xschr22>, e).[48]

In addition, other classes of bidentate imines were next shown to be efficient transient directing mediators, *ortho*-sulfinyl aniline being a representative example as reported by the groups of He and Chen. In this case also, the reaction would proceed via a fairly stable fused 5,5-membered palladabicycle that could be isolated as its acetate complex in 85^% and further characterized by X-ray diffraction analysis (Scheme^^22<xschr22>, f).[49] Overall, these processes presumably proceeded through a similar mechanism, as depicted in Scheme^^21<xschr21>.

Finally, a related strategy in which the functions are reversed has been reported by the Kamenecka group which could perform the arylation of phenylglycine esters in the presence of an aromatic aldehyde as the transient directing mediator.[50]

In 2017, the Sorensen group pushed the process a step further by developing a double C($sp^2$)<C->H activation method for the straightforward synthesis of fluorenones from benzaldehydes and iodoarenes. In this process, anthranilic acid was shown to be the most efficient transient directing mediator to promote both activations and deliver the corresponding fluorenones in moderate yields (Scheme^^23<schr23>).[51a] In their exploration of the mechanism, the authors could isolate one of the two key palladacycles in 69^% yield. Thereby, the mechanism was proposed to proceed through two synergistic Pd(II)/Pd(IV) - Pd(II)/Pd(0) catalytic cycles and would first involve the imine condensation prior to palladium coordination and subsequent CMD to cleave the first C<C->H bond. The resulting first key fused 5,6-membered palladabicycle would undergo an oxidative addition with the

aryl iodide to deliver the corresponding Pd(IV) species. Subsequent reductive elimination and further ligand exchange would afford an arylated Pd(II) complex, which would subsequently undergo a second C<C->H palladation via CMD yielding the second key fused 6,7-membered palladabicycle. Nucleophilic cyclization via imine insertion and further β-hydride elimination would eventually occur to deliver both the imino-fluorenone product and the corresponding palladium(II) hydride species. The former would afford the desired fluorenone upon hydrolysis, thus regenerating the transient directing mediator, while the latter would yield a palladium(0) species through reductive elimination that could eventually be reoxidized by AgTFA.

About two years later, the groups of Li and Zhang extended the process to the use of arenes as coupling partners, using a monodentate transient directing mediator and potassium persulfate as the stoichiometric reoxidant. Thereby, the authors could synthesize various fluorenones using $Pd(OAc)_2$ along with 3,5-bis-(trifluoromethyl)aniline transient directing mediator in HFIP at 80^°C in moderate yields (Scheme^^24<schr24>).[51b] A plausible mechanism was proposed to be similar to the one depicted in Scheme^^23<xschr23>, albeit three C<C->H bonds are cleaved in this case.

One year after the initial report of Yu and Zhang on the direct arylation of benzaldehydes with aryl iodides relying on the use of α-methylalanine as the transient directing mediator (Scheme^^20<xschr20>), the Wang group could go one step further with this mediator and reported a direct dehydrogenative *ortho*-arylation of benzaldehydes with arenes utilized as both arylating agents and solvents. In this mild process, benzaldehydes are directly reacted with arenes and TFA at 60^°C in the presence of $Pd(OAc)_2$ and potassium persulfate as the stoichiometric oxidant promoting a Pd(II)/Pd(IV) catalytic cycle to deliver the corresponding *ortho*-arylated benzaldehydes in moderate to good yields (Scheme^^25<schr25>).[52] In their study, Wang and coworkers could demonstrate that the

catalytic cycle was operating through a fused 5,5-membered palladabicycle which could be isolated as its pyridine-complex and further reacted with the arene coupling partner under their standard reaction conditions to afford the desired product in 47^% yield. The mechanism was proposed to first involve the formation of the transient imine that would then coordinate to the palladium catalyst. Further C<C->H cleavage, presumably via a CMD process, would then yield the corresponding fused 5,5-membered Pd(II) bicycle whose oxidation with potassium persulfate would afford the corresponding electrophilic Pd(IV) complex that would react with the arene. A subsequent reductive elimination/hydrolysis would deliver the desired *ortho*-arylated benzaldehyde, thus regenerating both the Pd(II) catalyst and the transient aminoacid mediator. The same year, the Barrow group could elegantly apply this transient α-methylalanine-mediated *ortho*-arylation of benzaldehyde in the total synthesis of Boletopsin 11 as the key step of the synthesis.[53]

The dehydrogenative *ortho*-heteroarylation of benzaldehydes with heteroarenes can also be performed under rhodium catalysis using silver(I) oxide as the oxidant. In this case, a monodentate transient directing group is sufficient, enabling the use of a transient directing mediator as simple as benzylamine in combination with $[Cp^*RhCl_2]_2$ as the catalyst. In this process, various benzaldehydes as well as benzothiophene- and thiophene- 3-carbaldehydes could be heteroarylated in moderate to good yields (Scheme^^26<schr26>).[54] As a note, the authors could observe that the substrates underwent a double C<C->H activation towards benzo[4,5]thieno[3,2-*c*]isoquinolines under the reaction conditions with a range of benzothiophenes when using β-alanine as the transient directing mediator in HFIP.

While imine-transiently directed arylation reactions have revealed over the years to be remarkably efficient, the same holds true for alkylation reactions for which imines are also remarkably efficient transient directing groups. These alkylation reactions will be overviewed in the following section.

#### 4.1.2.2. Alkylation reactions

Needless to say that the alkylation of arenes is one of the most important transformations reported to date, alkylated arenes being key molecules utilized not only in organic synthesis but also in many other research areas such as medicinal chemistry, the agrochemical industry as well as polymer and material sciences. While the alkylation of arenes mainly relies on the venerable Friedel and Crafts reaction,[55] or C<C->H directed and innate direct alkylation reactions,[56] another strategy has emerged to promote the straightforward alkylation of C($sp^2$)<C->H bonds and lies in the use of transient imine-directing groups.

The first example of a direct C($sp^2$)<C->H bond alkylation of arenes has been reported back in 2000 when the Jun group could perform the double alkylation of both C($sp^2$)<C->H bonds of the carbonyl and the phenyl ring in benzaldehyde with different alkenes as alkylating agents in moderate to high yields using benzylamine and 2-amino-3-picoline as the transient directing mediators in the presence of Wilkinson's catalyst neat at 170^°C [Scheme^^27<schr27>, Eq.^^(1)].[57a] Two years later, they could extend the process to the direct alkylation of various aromatic ketones with unactivated aliphatic alkenes as alkylating agents. In this process, substrates are treated with catalytic amounts of benzylamine in the presence of Wilkinson's catalyst at 150^°C to deliver the corresponding alkylated aromatic ketones in high yields, though the process suffers from a rather limited substrate scope [Scheme^^27<xschr27>, Eq.^^(2)].[57b] As a note, a microwave-activated version was reported for the alkylation of acetophenone with 1-decene in the presence of Wilkinson's catalyst, benzylamine and zinc chloride neat at 170^°C.[57c] This alkylation could also be performed with a rhenium catalyst using *para*-anisidine as the transient directing mediator and acrylates as alkylating agents: in this case, conjugated indenes, resulting from an in^^situ

insertion into the transient imine, reductive elimination and further elimination of the transient directing mediator, were formed.[58]

When performed in an intramolecular fashion, the *ortho*-alkylation of benzaldehydes bearing a remote alkene moiety proved to be efficient and provides an efficient entry to a range of heterocycles. In this perspective, 3-allyloxy- and protected 3-allylamino-benzaldehydes or aryl ketones could be cyclized into the corresponding indolines and 2,3-dihydrofurans in moderate to excellent yields under rhodium catalysis using β-alanine as the transient directing mediator [Scheme^^28<schr28>, Eq.^^(1)].[59a] An enantioselective version of the process could further be developed using chiral benzylamine type transient directing mediators under ruthenium catalysis [Scheme^^28<xschr28>, Eqs.^^(2) and (3)].[59b,c] The asymmetric induction model was postulated to rely on a rigidified conformation resulting from an estimated limited distance of 3.1^^Å between the top arene ligand and the C<C->N bond preventing the latter from rotating. Thereby, the conformation of the chiral amine transient directing mediator being blocked, the alkene moiety would therefore approach the ruthenacycle from its less hindered face with its hydrogen atom pointing towards the top arene ligand to minimize steric clash. The resulting coordination and further 1,2-migratory insertion would eventually lead to the formation of the favored enantiomer. The Zhang group also reported that ruthenium catalysis was highly efficient for such alkylation processes and developed an efficient *ortho*-alkylation of benzaldehydes with *N*-alkyl-maleimides. In this case, while bidentate glycine and 2-aminobenzoic acid gave no reactivity, monodentate disubstituted anilines leading to the formation of stable 5-membered ruthenacycles provided good yields and selectivity, 2-methyl-3-(trifluoromethyl)aniline being the best transient directing mediator due to the combination of its ideal electronic and steric properties. In this process, benzaldehydes are reacted with 1.5^^equiv. of various *N*-alkyl-maleimides in the presence of $[Ru(p\text{-cymene})Cl_2]_2$, catalytic amounts of the aniline transient directing mediator in a mixture of 1,2-dichloroethane and HFIP at 60^°C to deliver the corresponding *N*-

alkylsuccinimide-substituted benzaldehydes in moderate to good yields (Scheme^^29<schr29>).[60] The mechanism was proposed to first proceed by the imine formation prior to C<C->H activation and further maleimide coordination. Subsequent insertion and protonolysis would deliver the alkylated aromatic imine while regenerating the ruthenium catalyst. Hydrolysis would eventually occur to afford the final alkylated benzaldehyde and to close the catalytic cycle.

Alkenes are not the only reaction partners that can be used as demonstrated by Chen and Sorensen who took advantage of transient imines formation from aniline and (hetero) aromatic aldehydes to develop an elegant double *ortho*-alkylation process, the mono-alkylation being much more difficult to achieve with sufficient selectivity, involving potassium trifluoroalkylborates as alkylating agents. Catalytic amounts of $[Cp^*IrCl_2]_2$ and aniline as a monodentate transient directing mediator in the presence of catalytic $AgNTf_2$ and stoichiometric silver fluoride oxidant in acetic acid at 100^°C led to the formation of the corresponding di-*ortho*-alkylated desired aldehydes in good to excellent yields. Most interestingly, the key 5-membered iridacycle could be isolated in 63^% and further characterized by X-ray diffraction analysis [Scheme^^30<schr30>, Eq.^^(1)].[61] As an interesting extension, the methylation of various benzaldehydes with potassium methyltrifluoroborate was next reported using palladium catalysis. Bidentate orthanilic acid was found to be a suitable transient directing mediator resulting in the formation of a stable fused 5,6-membered palladabicycle. In this process, the authors used $Pd(OAc)_2$ as the metallic catalyst along with fluoro-2,4,6-trimethylpyridinium tetrafluoroborate as the oxidant in a 9^:^1 mixture of HFIP and TFA to obtain the corresponding methylated benzaldehydes in moderate to good yields [Scheme^^30<xschr30>, Eq.^^(2)].[62] Here again, the key 5,6-membered palladabicycle intermediate, stabilized by coordination of triphenylphosphine, could be isolated and characterized.

Another and last class of alkylating agents reported for the transient imine-mediated alkylation of C($sp^2$)<C->H bonds in arenes are allylic acetates and phosphonates. Indeed, the Shi group reported an elegant atroposelective alkylation of C($sp^2$)<C->H bonds in biaryls bearing an aldehyde functional group. L-*tert*-Leucine was used as the homochiral transient directing mediator while allylic esters and carbonates or Morita-Baylis-Hillman carbonates were used as allylating agents to deliver the corresponding allylated chiral biaryls through dynamic kinetic resolution and oxygen β-elimination in moderate to high yields and excellent enantioselectivity. In this process, $Pd(OAc)_2$, along with sodium butanoate in a mixture of HFIP and HOAc, was shown to provide the most efficient catalytic system [Scheme^^31<schr31>, Eqs.^^(1) and (2)],[63a] which could further be slightly modified to extend the scope of the process.[63b]

As a note, other alkylation agents can be used, such as aldehydes that can insert in the C<C->H activated rhodacycle complex yielding phthalides resulting from an in^^situ condensation followed by β-hydride elimination, a reaction that can even be done in an enantioselective manner when using a chiral benzylic amine as the transient directing mediator,[64] or cyclopropanols through palladium-catalyzed ring-opening for atroposelective processes.[65]

If the transient imine-directed alkylation of C($sp^2$)<C->H bonds in arenes provides a useful and efficient alternative to more classical processes for the synthesis of alkylated arenes, despite some processes being still of too narrow scope, the use of transient imines for the functionalization of arene C($sp^2$)<C->H bonds was also met with quite some success for related alkenylations that will now be overviewed.

#### 4.1.2.3. Alkenylation reactions

The first example of a transient imine-directed *ortho*-C<C->H alkenylation of arenes, namely (hetero)aromatic aldehydes, with activated acrylates and styrene, has been reported in

2018 by the group of He and Wang using rhodium catalysis. In this process, *para*-toluenesulfonamide was used as the transient directing mediator along with copper acetate hydrate as the stoichiometric oxidant, and catalytic $AgSbF_6$ in 1,2-dichloroethane, leading to the formation of the corresponding mono-alkenylated (hetero)aryl aldehydes in moderate to good yields (Scheme^^32<schr32>).[66] The mechanism was believed to proceed first by the formation of the *N*-tosyl-imine which would subsequently coordinate to the $RhCp^*(SbF_6)_2$ active catalytic species. Further C<C->H activation would lead to the formation of a stable 5-membered rhodacycle onto which the activated alkene coupling partner could coordinate prior to its insertion to yield the corresponding 7-membered rhodacycle. β-Hydride elimination and further hydrolysis would eventually occur to deliver both the product and Rh(I)Cp* which would be reoxidized by $Cu(OAc)_2$^<M.>^$H_2O$ in combination with $AgSbF_6$ to close the catalytic cycle.

Noteworthy, this process is not limited to aromatic aldehydes since the remote δ-$C(sp^2)$<C->H olefination of β-aryl substituted aliphatic aldehydes could recently be achieved by the Su group under palladium catalysis, using however an enamine transient directing group by adding catalytic secondary amines, with oxygen acting as the terminal oxidant, in good yields (Scheme^^33<schr33>).[67]

Still, the pioneering study of He and Wang paved the way for further developments, on more specific substrates however, but sometimes with more interesting regioselectivities. Indeed, the Maiti group reported an elegant remote $C(sp^2)$<C->H olefination of (hetero)biaryl aldehydes and anilines using transient imines as linchpin, by finely designing and tuning their transient aniline and aldehyde mediators, embedded with a pyrimidine moiety enabling a distal coordination of the palladium catalyst to reach the desired $C(sp^2)$<C->H bond to be activated, with impressive levels of regioselectivity. Thereby, various (hetero)biaryl aldehydes and anilines could be remotely alkenylated with activated alkenes using palladium

catalysis along with monoprotected aminoacid ligands developed by the Yu group,[68] silver carbonate and copper(II) acetate oxidant in 1,2-dichloroethane at 100^°C in moderate to good yields [Scheme^^34<schr34>, Eqs.^^(1) and (2)].[69]

Atroposelective processes have also been developed based on the use of homochiral aminoacids as transient directing mediators. Indeed, the Shi group reported in 2017, the atroposelective C($sp^2$)<C->H olefination of various biaryl aldehydes with different acrylates and styrenes via (dynamic) kinetic resolution (DKR). In this process, the use of L-*tert*-leucine as the chiral transient directing mediator enabled an impressive control of the enantioselectivity along with high to excellent yields when combined with catalytic amounts of $Pd(OAc)_2$, and benzoquinone together with HFIP and HOAc at 60^°C (Scheme^^35<schr35>).[70] The high levels of enantioselectivity could be attributed to an efficient dynamic kinetic resolution induced by the steric clash between the *tert*-butyl group embedded in the transient imine directing group and the second aryl moiety, thereby favoring the least hindered conformation of the imine intermediate out of the two possible. As a note, this process was also extended to 3-arylbenzothiophenes and -furans,[63b] 2-aryl-enals, *N*-arylindole-2-carboxaldehydes,[71,72] as well as cyclopropanols and vinylcyclopropanes as alkenylation reagents.[65]

The synthetic utility of this process was further highlighted as a key step in the total synthesis of the anticancer agent TAN-1085 that featured a highly atroposelective palladium-catalyzed olefination of a properly functionalized biaryl aldehyde with butyl acrylate. In this key transformation, a $Pd(OAc)_2$, L-*tert*-leucine, silver(II) carbonate catalytic system in a mixture of HFIP and AcOH was selected to deliver the corresponding intermediate in 75^% yields and 99^% *ee* (Scheme^^36<schr36>).[73]

In all these processes, a stoichiometric oxidant is required for the catalytic cycle to proceed, a limitation that was elegantly tackled by the Ackermann group which managed to

push further the boundaries of the enantioselective biaryl functionalization field by combining palladium-aminoacid cooperative catalysis and electrochemistry. Performing such alkenylations in an electrolytic cell indeed enables to avoid using these stoichiometric terminal oxidants and the atroposelective C($sp^2$)<C->H olefination of various biaryl aldehydes and *N*-aryl pyrroles could therefore be performed using catalytic amounts of $Pd(OAc)_2$ and L-*tert*-leucine together with substoichiometric amounts of lithium acetate (LiOAc) as an electrolyte additive in acetic acid under constant current electrolysis (CCE) at 1^^mA (graphite felt (GF) anode, platinum plate cathode) at 60^°C in fair to good yields and high enantioselectivity [Scheme^^37<schr37>, Eqs.^^(1) and (2)].[74] Supported by both experimental and computational data, once the imine formed and the palladium metallic center coordinated, the mechanism is believed to proceed by the C($sp^2$)<C->H activation of the aryl moiety to promote the formation of a favored fused 5,7-membered palladabicycle over its 5,5 counterpart, higher in energy. Subsequent ligand exchange between acetic acid and the alkene would then occur to further enable its insertion. β-Hydride elimination prior to hydrolysis would then eventually deliver the desired alkenylated biaryl while generating palladium(0) to be reoxidized into palladium(II) through constant-current electrolysis (CCE). Noteworthy, the authors finally reported the syntheses of helicenes and BINOLs in good yields and high enantioselectivity using this strategy.

Finally, the Maiti and Volla groups, in continuation of their studies on the C4 arylation of indole-3-carbaldehydes, reported that such compounds could also be alkenylated at the same position with an iodinated acrylate in moderate yields (Scheme^^38<schr38>).[43]

As final notes for this section, the Cheng group reported in 2013 a rhodium-catalyzed annulation of benzaldehydes with alkynes through hydrazone-directed *ortho*-C<C->H activation, using acetyl hydrazine as the transient directing mediator to deliver the corresponding indenones in moderate to good yields.[75] Similar products could also be

obtained through rhenium(I) catalysis, as demonstrated by the group of Kuninobu and Takai, using benzaldehydes as both the substrates and the coupling partners and *N*-acetyl-aniline as the transient directing mediator to form a transient hemiaminal directing group.[76] Sulfonamide-substituted indenes could also be synthesized using this annulation strategy from *N*-sulfonyl imines and alkynes under ruthenium catalysis using a catalytic amount of *para*-toluenesulfonamide to generate a transient aminal directing group.[77] Finally, it ought to be noted that transient nitrosamines could also be demonstrated as efficient directing groups for the rhodium-catalyzed synthesis of indoles starting from anilines and alkynes, as disclosed by the Su group, using isoamyl nitrite as the transient directing mediator (Scheme^^39<schr39>).[78]

While transient imine-directed olefination reactions have proven their efficiency, especially for the straightforward synthesis of axially chiral alkenylated bi(hetero)aryls, some efforts have been conducted to promote the alkynylation of such substrates and will therefore be briefly overviewed in the following section.

#### 4.1.2.4. Alkynylation reactions

Based on their above-discussed work on enantioselective alkenylation of bi(hetero) aryl aldehydes (Scheme^^35<xschr35>), the Shi group reported the alkynylation of these substrates under similar conditions. Indeed, in 2018, on their way to the syntheses of (+)-isoschizandrin and (+)-steganone, they could perform the enantioselective alkynylation of biaryl aldehydes through desymmetrization and (dynamic) kinetic resolution in good to excellent yields and enantioselectivity using various (bromoethynyl)trialkylsilanes as alkynylating agents in acetic acid at 60^°C. In this process, the use of $Pd(OAc)_2$ along with L-*tert*-leucine as the chiral transient directing mediator, AgOAc and $KH_2PO_4$ to buffer the medium was shown to be the most efficient catalytic system [Scheme^^40<schr40>, Eq.^^(1)].[79a] With a slight modification of the reaction conditions, this transformation could

be extended to the atroposelective alkynylation of various biheteroaromatic aldehydes in high to excellent yields and enantioselectivity [Scheme^^40<xschr40>, Eq.^^(2)].[79b]

More recently, the group of Echavarren could extend this process to a broadly applicable achiral *ortho*-alkynylation of benzaldehydes with TIPS-protected bromoalkynes using an aniline transient directing mediator under rhodium(III) catalysis at room temperature (Scheme^^41<schr41>).[80]

As overviewed with all reactions covered in the previous sections, the use of transient imine directing groups has enabled the design and development of a set of efficient and straightforward synthetic tools for the alkylation, alkenylation and alkynylation of C($sp^2$)<C->H bonds in a range of substrates. These reactions are however not limited to the formation of carbon-carbon bonds since many heteroatoms can also be introduced as highlighted in the next sections, starting with amination reactions.

#### 4.1.2.5. Amination reactions

Reactions enabling the formation of C($sp^2$)<C->N bonds are indeed among the most studied and utilized in the field of metal-catalyzed cross-couplings.[81] While the most classical strategy relies on the palladium- or copper- catalyzed amination of aryl (pseudo) halides, the direct amination of C($sp^2$)<C->H bonds is more appealing and has attracted a great deal of attention. In this context, the use of transient imine directing groups has also been elegantly applied and has resulted in the development of quite efficient processes, even if the direct introduction of non-protected amines still remains elusive. In sharp contrast, sulfonamides can be conveniently introduced, as demonstrated as early as 2016 by the group of Shi which reported the first straightforward *ortho*-sulfonamidation of benzaldehydes. The authors could indeed perform such a transformation by the mean of iridium catalysis -- using $[IrCp^*Cl_2]_2$ as the catalyst along with $AgPF_6$ as the chloride scavenger -- with arylsulfonyl azides using a catalytic amount of a 3-(trifluoromethyl)aniline transient directing mediator in

1,2-dichloroethane at 100^°C to deliver the corresponding products in good to high yields, though limited to electron-poor benzaldehydes (Scheme^^42<schr42>, a).[82a] The authors could furthermore isolate and characterize a key metallacycle intermediate, gaining interesting insights into the reaction mechanism.

Concomitantly, Yu and coworkers could report, in continuation of their studies on diverse *ortho*-C($sp^2$)<C->H functionalizations of benzaldehydes, a similar process using 2-fluoro-5-(trifluoromethyl)aniline as the transient directing mediator. Upon slight modifications of the catalytic system, the authors could decrease by half the temperature of the reaction to deliver the desired sulfonamides in good yields (Scheme^^42<xschr42>, b).[41] This process has also been reported by the groups of He and Chen using 3,5-di(trifluoromethyl)aniline as the transient directing mediator in 1,2-dichloroethane at 80^°C to yield the products in good to excellent yields (Scheme^^42<xschr42>, c).[82b] Eventually, the Rasheed group could replace the iridium catalyst with [Ru(*p*-cymene)$Cl_2$]$_2$ using similar trifluoromethyl substituted anilines or bidentate anthranilic acid as transient directing mediators in 1,2-dichloroethane or ethanol at 80^°C to afford both aryl- and alkyl-sulfonamidated benzaldehydes in moderate to excellent yields (Scheme^^42<xschr42>, d).[82c]

These transformations are believed to share the mechanism depicted in Scheme^^43<schr43>, starting first with the condensation of the aniline transient directing mediator onto the benzaldehyde substrate to form the corresponding imine moiety that would coordinate the activated monomeric iridium or ruthenium catalyst. Subsequently, the *ortho*-C<C->H activation would occur to deliver a 5-membered metallacycle that could further coordinate the sulfonyl azide coupling partner. Upon nitrogen release, the latter could be inserted to afford a second 6-membered metallacycle of which the metallic species would decoordinate via protonolysis to both regenerate the catalyst and yield the functionalized transient imine species. Hydrolysis of the latter would eventually occur to deliver the desired

*ortho*-functionalized benzaldehyde and the transient directing mediator (Scheme^^43<xschr43>).

From a synthetic perspective, the direct introduction of an amide might be more appealing and impactful, which can actually be performed using dioxazolones and various metallic catalysts along with an aniline transient directing mediator. The Jiao group was actually the first to report in 2018 such a transformation taking advantage of rhodium(III) catalysis in the presence of 4-(trifluoromethyl)aniline as the transient directing mediator to enable the formation of a range of *ortho*-amidated benzaldehydes in chlorobenzene at 120^°C in good to excellent yields (Scheme^^44<schr44>, a).[83a] Dong and coworkers next reported a similar process in which a transient amine mediator is not needed to form the transient imine in^^situ. In this case, the dioxazolone coupling partner also serves as a transient directing mediator generator delivering an imine by decarboxylation to an arylisocyanate that adds onto the starting benzaldehyde and yield the corresponding imine after further decarboxylation. On top of the use of the same $[RhCp^*Cl_2]_2/AgSbF_6$ catalytic system, the authors added catalytic amounts of zinc acetate dihydrate as an additive and a stoichiometric amount of benzoic acid to run the reaction in 1,2-dimethoxyethane at 120^°C and deliver the corresponding *ortho*-amidated benzaldehydes in moderate to good yields (Scheme^^44<xschr44>, b).[83b] Concurrently, the group of Prabhu also reported in 2018 a comparable method using $RhCp^*(OAc)_2/AgPF_6$ or $[RhCp^*Cl_2]_2/AgSbF_6$, however in the presence of catalytic amounts of 3,5-ditrifluoromethylaniline as the transient directing mediator in trifluoroethanol to extend the scope of the reaction to aromatic ketones and deliver the corresponding desired products from both aromatic ketones and aldehydes in moderate yields (Scheme^^44<xschr44>, c).[83c] Cobalt catalysis was also shown to be efficient for this transformation, as demonstrated by the groups of Wu, Li and Sundararaju who reported that combinations of $CoCp^*(MeCN)_3(SbF_6)_2$ and 4-chloroaniline (Scheme^^44<xschr44>, d)[83d] or $CoCp^*(CO)I_2/AgSbF_6$ and aniline

(Scheme^^44<xschr44>, e),[83e] respectively, were efficient for the amidation of benzaldehydes with different dioxazolones.

The shared mechanism of these transformations, apart from the amidation reported by the group of Dong with in^^situ transient directing mediator generation, was believed in all cases to start with the condensation of the aniline derivative onto the benzaldehyde to form the transient imine substrate that would subsequently be subjected to an *ortho*-C<C->H activation by the metallic catalyst to deliver a 5-membered metallacycle. Further coordination of the dioxazolone coupling partner followed by its insertion through decarboxylation would afford a second 6-membered metallacycle intermediate from which the metallic catalyst would be decoordinated via protonation and therefore regenerated to yield the corresponding amidated benzaldimine. Imine hydrolysis would eventually occur to deliver both the desired product and the transient directing mediator (Scheme^^45<schr45>).

More recently, the direct introduction of ureas[84] and phthalimides[85] was reported, using carbamoyl azides and *N*-tosyloxyphthalimides as the amination agents, respectively, both along with a monodentate aniline transient directing mediator. Although the former process mainly used pre-installed directing groups -- starting from benzamides -- a transiently directed version could be developed using 3,5-di(trifluoromethyl)aniline as the transient directing mediator enabling the installation of a urea moiety in a promising 51^% yield [Scheme^^46<schr46>, Eq.^^(1)]. As for the imidation process, the authors opted for ruthenium catalysis along with 2-fluoro-5-(trifluoromethyl)aniline as the transient directing mediator to deliver the corresponding *ortho*-imidated benzaldehydes in good yields [Scheme^^46<xschr46>, Eq.^^(2)].

Different cyclic scaffolds such as acridines could also be obtained via transient imine-directed amination of benzaldehydes thanks to the use of nitrosoarenes as coupling partners. The Cheng group indeed reported in 2017 the rhodium-catalyzed cyclization of those

substrates in the presence of benzylamine as the transient directing mediator, offering an efficient and straightforward entry to unsymmetrical acridines [Scheme^^47<schr47>, Eq.^^(1)].[86a] This process was further extended to the use of aromatic azides as the coupling partner by the Wang group to deliver, in a greener γ-valerolactone solvent, similar unsymmetrical acridines in similar yields.[86b] Eventually, Park, Kim and coworkers released a comparable method for the formation of 4-acylacridines using however 3-arylanthranils as both the coupling partners and the transient directing mediator generator upon opening with acetic acid into 2-benzoylanilines [Scheme^^47<xschr47>, Eq.^^(2)].[86c]

While the formation of C($sp^2$)<C->N bonds has been shown to be rather efficient for the amination of benzaldehydes under the transient imine directing strategy, the latter has also demonstrated high efficiency for the formation of C($sp^2$)<C->X and C($sp^2$)<C->O bonds that will be now be discussed.

#### 4.1.2.6. Halogenation reactions

As from 2017, some efforts have also been directed to take advantage of the transient imine directing strategy for the direct halogenation of C($sp^2$)<C->H bonds, the resulting halogenated arenes being important building blocks in organic synthesis as well as in medicinal chemistry. In continuation of their studies on the *ortho*-C($sp^2$)<C->H functionalization of benzaldehydes using transient directing groups, the groups of Yu and Zhang reported an efficient and simple direct *ortho*-chlorination and -bromination of benzaldehydes, a synthetic transformation that nicely complements their classical halogenation at the *meta*-position using aromatic electrophilic substitutions. Thanks to palladium catalysis along with the use of catalytic amounts of functionalized anilines -- namely 2-aminobenzoic acid for chlorination and 2-amino-4-nitrobenzoic acid for bromination -- as bidentate transient directing mediators, the authors could report both the *ortho*-chlorination and -bromination of a broad range of benzaldehydes in rather excellent

yields using *N*-chlorosuccinimide and *N*-bromosuccinimide, respectively, in either 1,2-dichloroethane or a 1^:^1 mixture of 1,2-dichloroethane and trifluoroacetic acid at 60 to 90^°C [Scheme^^48<schr48>, Eqs.^^(1) and (2)].[41]

In a similar vein, the group of Zhang disclosed in 2019, in two separate reports, both the palladium-catalyzed *ortho*-chlorination and -bromination of benzaldehydes using similar reaction conditions using trifluoromethylated anilines as transient directing mediators to deliver the corresponding chlorinated and brominated benzaldehydes in good to excellent yields [Scheme^^49<schr49>, Eqs.^^(1) and (2)].[87] In the chlorination case, the addition of a pyridinone ligand was beneficial. As for the mechanism of the chlorination transformation, Zhang and coworkers proposed it to start with the condensation of the aniline mediator onto the benzaldehyde substrate to form the transient imine that will further coordinate the palladium catalyst before activating the *ortho*-C<C->H bond. An oxidative addition of *N*-chlorosuccinimide would subsequently occur to generate a Pd(IV) metallacycle intermediate that would further undergo a reductive elimination to both regenerate the Pd(II) catalyst and deliver the chlorinated transient imine. Hydrolysis of the directing group would eventually afford the desired functionalized benzaldehyde product while releasing the transient directing mediator.

Remarkably, the *ortho*-fluorination of benzaldehydes under palladium catalysis could also be achieved as reported by the groups of Sorensen and Chen in 2018. Key to the success of this reaction, the use of 1-fluoro-2,4,6-trimethylpyridinium triflate acting as both an electrophilic fluorinating agent and stoichiometric oxidant required for the catalytic cycle to be operative, was found to be optimal along with catalytic amounts of $Pd(OAc)_2$ and aniline-2,4-disulfonic acid as the transient directing mediator to deliver the desired fluorinated benzaldehydes in moderate to good yields [Scheme^^50<schr50>, Eq.^^(1)].[62] This fluoropyridinium salt could further be substituted for NFSI, as demonstrated by the Lou and

Xu group in 2021. This process, employing an iminocarbamate transient directing group and silver nitrate as the co-oxidant along with NFSI, notably enabled the formation of fluorinated aromatic ketones in high yields, nicely complementing the first method [Scheme^^50<xschr50>, Eq.^^(2)].[88]

#### 4.1.2.7. C($sp^2$)<C->O bond formation

Contrary to the formation of C($sp^2$)<C->X bonds, little work has yet been devoted to the formation of C($sp^2$)<C->O bonds by transient imine directing strategies despite the synthetic usefulness of such transformations. Indeed, two groups -- namely the groups of Sorensen and Zhang -- could so far report methods for the *ortho*-hydroxylation and -methoxylation, respectively, of benzaldehydes. The former disclosed in 2017 the straightforward hydroxylation of benzaldehydes with *para*-toluene sulfonic acid thanks to palladium catalysis in combination with an aniline transient directing mediator. Indeed, treating a range of benzaldehydes with *p*-TsOH in the presence of $Pd(OAc)_2$ along with 2-amino-4-chlorobenzoic acid as the transient directing mediator and 1-fluoro-2,4,6-trimethylpyridinium triflate as the oxidant in acetic acid at 90^°C led to the formation of the corresponding salicylaldehydes in moderate yields (Scheme^^51<schr51>).[89] The authors could isolate the key palladium intermediate in 60^% yield as a 4-*tert*-butylpyridine complex with a stoichiometric amount of $Pd(OAc)_2$ in HFIP at 100^°C. Thereby, the mechanism of the transformation was believed to start first with the condensation of the aniline onto the benzaldehyde moiety to form the corresponding transient imine substrate. Subsequent coordination of the palladium catalyst followed by C<C->H activation would deliver a fused 5,6-membered palladacycle further oxidized by fluorination with 1-fluoro-2,4,6-trimethylpyridinium triflate. Subsequently, a ligand exchange with *p*-TsOH would occur to displace the fluorine atom and allow a reductive elimination to take place prior to decoordination of the palladium catalyst, thereby delivering the *ortho*-tosylated transient

imine product. Eventually, a first hydrolysis would free the benzaldehyde moiety while a second one would furnish the desired hydroxylated product upon release of *p*-TsOH. As a note, the authors further reported an example of perfluoalkoxylation in a promising 22^% yield as well as unusual reactivity resulting in the formation, with 56^% yield, of an *ortho*-chlorinated byproduct, 1,2-dichloroethane probably acting as a chlorinating agent in this case. Also, a similar hydroxylation process recently extended the scope to polyaromatic aldehydes as reported by the Zhang group using a palladium(0) precatalyst along with orthanilic acid as the transient directing mediator for the C8-selective hydroxylation of 1-naphthaldehydes through trifluoroacetoxylation and subsequent hydrolysis employing a hypervalent iodine reagent ($PhI(OTFA)_2$).[90] Interestingly, *ortho*-acetoxylation using related PIDA could also be achieved provided the pre-installation of the imine directing group with an aniline.

About two years later, the group of Zhang reported a straightforward method for the formation of $C(sp^2)$<C->O bonds using a transient imine directing group, for the *ortho*-methoxylation of benzaldehydes. Indeed, upon reaction with methanol (20^^equiv.) in the presence of $Pd(OAc)_2$, along with 3-(trifluoromethyl)aniline as the transient directing mediator and potassium persulfate as the stoichiometric oxidant, a range of benzaldehydes could be *ortho*-methoxylated in dichloromethane at 60^°C in moderate yields (Scheme^^52<schr52>).[87a] As for the mechanism of the transformation, Zhang and coworkers proposed it to start with the condensation of the aniline mediator onto the benzaldehyde substrate to form the corresponding transient imine that would further coordinate the palladium catalyst activating the *ortho*-C<C->H bond. A double coordination of methanol through persulfate oxidation would subsequently occur to generate a Pd(IV) intermediate species that would further undergo a reductive elimination to both regenerate the Pd(II) catalyst and deliver the methoxylated transient imine. Hydrolysis of the latter would eventually afford the desired functionalized benzaldehyde product. As a note, the group of

Wang further extended this process to the perfluoroalkoxylation of these substrates under similar conditions, however using L-valine as the transient directing mediator.[91]

#### 4.1.2.8. Borylation, selenylation, silylation and deuteration reactions

In addition to arylation, alkylation, alkenylation, alkynylation, amination, halogenation and oxygenation reactions, other functional groups can be introduced directly by straightforward functionalization of C($sp^2$)<C->H bonds in benzaldehydes using the transient imine directing group strategies. Their *ortho*- and *meta*- selective borylations were indeed reported by the Chattopadhyay group in 2017 through the transient formation of an imine moiety that could coordinate either the iridium catalyst or a boron atom embedded in the iridium complex. Under classical iridium/$B_2Pin_2$ catalysis using either methylamine or *tert*-butylamine to generate the transient imine functional group, and depending on the ligand used, 8-aminoquinoline (8-AQ) or 3,4,7,8-tetramethyl-1,10-phenanthroline (TMP), a range of benzaldehydes could be selectively *ortho*- or *meta*- borylated, respectively, in good to excellent yields and levels of selectivity (Scheme^^53<schr53>).[92] In this case, the imine was not generated in^^situ but had to be generated upfront and the selectivity difference was here accounted for a different coordination of the transient imine to the iridium complex. While the *ortho*-borylation would result from the coordination of the nitrogen atom of the imine moiety to the iridium center, the *meta*-borylation would be due to the coordination of either the nitrogen or the hydrogen of the imine to a boron atom of an iridium-bound BPin moiety.

As a note, an impressive transition-metal-free version of this process, likely to involve an electrophilic aromatic substitution, has recently been disclosed by the Chatani group using *tert*-butylamine as the transient directing mediator and boron tribromide as the borylating agent.[93]

Later on, the groups of Zhou and Zhang jointly disclosed the direct *ortho*-C<C->H selenylation of benzaldehydes using palladium catalysis in combination with a transient directing group. In this report, the authors utilized diaryl diselenides, $Pd(OAc)_2$ as the catalyst along with benzidine as the transient directing mediator in the presence of copper(II) bromide as the stoichiometric oxidant in DMF at 80^°C to furnish the desired *ortho*-C<C->H selenylated benzaldehydes in moderate to good yields (Scheme^^54<schr54>).[94] On the basis of a series of control experiments and mechanistic studies, the authors proposed a mechanism operating through three different pathways, which could occur concomitantly, all starting by the condensation of the transient directing group onto the benzaldehyde substrate to install the transient imine whose *ortho*-C($sp^2$)<C->H bond activation would deliver a 5-membered palladacycle. At this point, either an oxidative addition of the diaryl diselenide could occur to afford the corresponding Pd(IV) species (path a) or a ligand exchange could take place with an arylselenol that would be generated further in the mechanism to yield the corresponding Pd(II) species (path b). The Pd(IV) palladacycle could subsequently undergo a reductive elimination towards the desired *ortho*-selenylated transient imine upon release of an acetoxy(phenylselenyl)palladium(II) species that could either furnish an arylselenol entity -- potentially converted back into diaryl diselenide by $CuBr_2$ oxidation -- through ligand exchange with acetic acid while regenerating $Pd(OAc)_2$, or undergo further *ortho*-C<C->H activation with the starting transient imine to deliver the aforementioned Pd(II) species generated through path b (path c). Finally, reductive elimination of the latter would thereby release both the desired *ortho*-selenylated transient imine and a Pd(0) species to be reoxidized into Pd(II)$(OAc)_2$ by copper(II) bromide in the presence of acetic acid. Hydrolysis of the *ortho*-functionalized imine would eventually occur to deliver the desired product along with benzidine.

In addition to borylation and selenylation, the directed silylation of benzaldehydes has also been reported. Indeed, the group of Shi developed an efficient *ortho*-silylation of

benzaldehydes with hexamethyldisilane that proceeded without racemization when starting from axially chiral biaryl aldehydes. In this process, the authors used palladium catalysis along with a β-aminoacid -- namely 3-amino-3-phenylpropionic acid -- as the transient directing mediator in the presence of substoichiometric amounts of a benzoquinone derivative as the oxidant and lithium acetate as an additive to perform the *ortho*-silylation of the starting benzaldehydes in a 1^:^1 mixture of HFIP and acetic acid at 60^°C in good yields (Scheme^^55<schr55>).[95] To further demonstrate the synthetic utility of this process, the obtained silylated benzaldehydes could be further post-functionalized by either halogenation or Hiyama coupling. As for the mechanism of the transformation, the authors suggested first a condensation of the β-aminoacid onto the aldehyde moiety to furnish the corresponding imine that would coordinate the palladium catalyst. Subsequent C<C->H activation would afford a fused 5,6-membered palladabicycle that could undergo an oxidative addition with hexamethyldisilane to generate a Pd(IV) intermediate which would subsequently release the silylated transient imine upon reductive-elimination. Eventually, the hydrolysis of the latter would yield the desired *ortho*-silylated benzaldehyde derivative while regenerating both $Pd(OAc)_2$ and the β-aminoacid mediator.

Last, the Beller group elegantly implemented the transient imine directing strategy to the *ortho*,*ortho'*-deuteration of (hetero)aromatic aldehydes with deuterium oxide under manganese catalysis. In this process, the authors opted for an aliphatic *n*-butylamine transient directing mediator, used in catalytic amounts, to afford the corresponding deuterated products in both excellent yields and levels of deuterium incorporation (Scheme^^56<schr56>).[96a] Noteworthy, a range of α,β-unsaturated aldehydes could also be deuterated. This deuteration reaction was recently extended to aromatic ketones using an aniline transient mediator and ruthenium catalysis.[96b]

While this last report closes our overview of the reactions that can be efficiently performed with a transient imine directing group for the functionalization of C($sp^2$)<C->H bonds in benzaldehydes, this strategy has also been shown to be rather fruitful for the direct functionalization of conjugated ketones and aldehydes: they will be discussed in the following section.

#### 4.1.3. C($sp^2$)<C->H bond functionalization in α,β-unsaturated ketones and aldehydes

On top of *ortho*-C<C->H bond functionalization of benzaldehydes, the transient directing strategy could also be used to trigger the activation of C($sp^2$)<C->H bonds embedded in α,β-unsaturated ketones and aldehydes, involving the formation of a transient enamine in this case. Back in 2002, the Jun group reported the selective β-alkylation of (*E*)-4-phenylbut-3-en-2-one with a range of unactivated terminal alkenes, used in large excess, through rhodium catalysis along with the catalytic use of diethylamine as the transient directing mediator. While the overall process, that relies on the use of Wilkinson's catalyst in the presence of catalytic amounts of benzoic acid in toluene at 130^°C, was shown to be rather efficient in terms of yields, the main drawback lies in the systematic formation of isomeric mixtures of α,β- and β,γ- unsaturated alkylated ketones, the latter being moreover formed without control over the stereochemistry of the double bond (Scheme^^57<schr57>).[97] Nonetheless, subjecting the mixture to heterogeneous hydrogenation would obviously deliver a single aliphatic ketone.

Enals were also shown to be suitable substrates for such transiently directed alkylations, as demonstrated by the Sorensen group which reported some preliminary studies on their β-C($sp^2$)<C->H alkylation with 4-(trifluoromethyl)aniline as the transient directing mediator in the presence of additional catalytic crotonic acid (Scheme^^58<schr58>).[61] Despite its limited efficiency and the unclear role of crotonic acid, this challenging

preliminary process offers an interesting straightforward entry to β-alkylated α,β-unsaturated aldehydes that clearly merits further investigations.

This last report closes the exhaustive overview of C($sp^2$)<C->H bonds functionalization using transient imine directing groups: a range of efficient and straightforward processes have been developed over the years and this is clearly still a stimulating and highly competitive area of research. This strategy has successfully been implemented for the functionalization of a range of C($sp^3$)<C->H bonds embedded in aliphatic aldehydes and ketones, as well as aliphatic amines, reactions that are the focus of the following section.

### 4.2. C($sp^3$)<C->H functionalization

While the area of C($sp^2$)<C->H bond functionalization through the use of transient directing groups has been extensively studied over the last decades, the activation of its C($sp^3$)<C->H counterpart has been much more challenging since the field could only see the first reports emerging in 2012. Fortified by the knowledge acquired through the development of plethora of processes -- above-reviewed -- for the transient imine-directed C($sp^2$)<C->H functionalization of aromatic aldehydes and ketones, the scientific community could indeed tackle the more challenging task of activating particularly inert C($sp^3$)<C->H bonds embedded in aliphatic aldehydes, ketones and amines with tremendous efforts provided throughout the last five years.[7i,j] The imine transient directing group having henceforth proven its value, it has been largely utilized to achieve C($sp^3$)<C->H bond functionalization of aliphatic aldehydes and ketones and will be overviewed in the following section.

#### 4.2.1. C($sp^3$)<C->H bond functionalization of aldehydes and ketones

The functionalization of unactivated C($sp^3$)<C->H bonds constitutes an important challenge in aliphatic aldehydes and ketones due to their lower rigidity and a significant

decrease in electronic activation when compared to aromatic aldehydes and ketones, without mentioning the underlying issues of both regio- and stereoselectivities. Yet, through thorough designs of different catalytic systems and transient directing mediators relying on a transient imine directing group, a range of transformations have been recently reported, the most widely studied one being certainly the arylation reaction which will be discussed in the next section of this review article, the transformations that will be discussed in this section being classified according to the nature of the C($sp^3$)<C->H bond to be arylated.

#### 4.2.1.1. (Hetero)arylation reactions

##### 4.2.1.1.1. Benzylic C($sp^3$)<C->H bond

A lot of reports in the area of C($sp^3$)<C->H bond functionalization of aldehydes and ketones deal with activation of benzylic positions: while of relatively limited synthetic relevance, significant advances could however be made, and interesting concepts have emerged from the activation of the benzylic C($sp^3$)<C->H bond in benzaldehyde derivatives. The group of Yu was actually the first one to showcase the efficiency of the transient imine directing group strategy with *ortho*-methylbenzaldehydes and could exploit the ability of aminoacids to generate efficient transient imines able to coordinate a palladium catalyst and therefore facilitate the (hetero)arylation at the benzylic position with a range of iodo(hetero) arenes in moderate to high yields [Scheme^^59<schr59>, Eq.^^(1)].[98] The authors could further demonstrate the efficiency of their process by substituting glycine for a chiral aminoacid, L-*tert*-leucine, and by slightly modifying their catalytic system to achieve enantioselective arylation of benzylic C($sp^3$)<C->H bonds in moderate to good yields and high levels of enantioselectivity, the main limitation being the use of electron-poor benzaldehydes and iodoarenes [Scheme^^59<xschr59>, Eq.^^(2)]. The rather elusive explanation for such levels of enantiocontrol was simply based on steric repulsion between the bulky *tert*-butyl group embedded in the transient directing group and the alkyl chain of the

benzaldehyde substrate, through the formation of the most favored fused 5,5-membered palladabicycle intermediate.

In a similar vein, the groups of Lei and Hu could report the same year the benzylic C($sp^3$)<C->H bond arylation of *ortho*-methylbenzylaldehydes using slightly different reaction conditions and acetyl hydrazine as the transient directing mediator in moderate to excellent yields (Scheme^^60<schr60>, a).[99] About two years later, the groups of Jung and Kim could demonstrate the efficiency of a tridentate transient directing mediator for such processes under similar conditions by performing benzylic C<C->H arylations with iodoarenes in moderate yields (Scheme^^60<xschr60>, b).[100] This set the stage for the publication of additional reports with either other transient directing mediators, whose relevance is sometime not obvious, or catalytic systems, six additional close reports being published in 2020 and 2021 alone. Indeed, while the groups of Li, and Liu and Lou could demonstrate the ability of semicarbazide[101] and 2-dimethylaminoethylamine,[102] respectively, to act as efficient transient directing mediators (Scheme^^60<xschr60>, c and d), the group of Bao extended the use of acetyl hydrazine as a transient directing mediator to alumina-supported nanoparticles of palladium(0) (Scheme^^60<xschr60>, e).[103] Eventually, the groups of Bhat, Li and Zhang could extend the method to the arylation of 3-methylheteroarene-2-carbaldehydes with L-valine (Scheme^^60<xschr60>, f),[104] to the use of glycinamide hydrochloride as a transient directing mediator (Scheme^^60<xschr60>, g)[105] and to the biarylation of *ortho*-methylbenzaldehydes with cyclic diaryliodonium salt reactants using L-*tert*-leucine (Scheme^^60<xschr60>, h),[106] respectively.

As for the mechanism of these transformations, they follow the one depicted in Scheme^^61<schr61> and would start with the condensation of the transient directing mediator onto the aldehyde moiety to furnish the corresponding imine that could further coordinate the palladium(II) active catalyst to generate a first Pd(II) metallacycle. Subsequent

C<C->H activation would occur to afford a bicyclic Pd(II) intermediate that could undergo an oxidative addition with the iodoarene or the biaryliodonium triflate to yield the corresponding Pd(IV) metallabicycle. Upon iodine extrusion with a silver salt, a reductive elimination would take place to both regenerate the Pd(II) active catalyst and deliver the transient (hetero) arylated imine product to be eventually hydrolyzed, thereby affording the desired product.

As final notes for this section, several methods could take advantage of these processes for the synthesis of anthracenes and other polycyclic aromatic hydrocarbons by promoting the annulation of *ortho*-methylbenzaldehydes and iodoarenes,[100,107] and benzylic C($sp^3$)<C->H arylation could also be achieved on thiophenol, using however an unusual transient protection of 2,4,6-trimethylbenzenethiol with ethyl acrylate prior to classical C($sp^3$)<C->H palladium-catalyzed arylation and in^^situ deprotection.[108]

#### 4.2.1.1.2. Unactivated C($sp^3$)<C->H bond

While limited to the synthesis of really specific benzylated benzaldehyde derivatives, the development of the processes discussed in the previous section however set the stage for the design and development of much broader processes for the arylation of unactivated C($sp^3$)<C->H bonds embedded in aliphatic aldehydes through the use of a transient imine directing group, a problem that was first tackled in 2016 by the groups of Li and Ge. Indeed, thanks to palladium catalysis and a β-alanine transient directing mediator, they could perform the β-arylation of a range of aliphatic aldehydes with various iodoarenes in moderate to good yields [Scheme^^62<schr62>, Eq.^^(1)].[109] A screening of various bidentate mediators revealed that only β-aminoacids were found to be efficient while α-aminoacids like glycine were shown to be totally inefficient, a transient fused 5,6-membered palladabicycle being therefore more favored. Interestingly, the arylation is not limited to methyl groups, although more favorable, since aliphatic aldehydes with long aliphatic chains could also be efficiently arylated at a methylene. To gain more insights into the reaction mechanism, the authors could

isolate the key fused 5,6-membered palladabicycle as its pyridine complex and further react it with the aryl iodide to deliver the desired arylated product.

Later on, the group of Bull could demonstrate the efficiency of an alternative transient directing mediator, *N*-tosylethylenediamine, not leading to the formation of a fused 5,6-membered palladabicycle in this case but to a 5,5-one. With this simple transient directing mediator in hands, the arylation of various aliphatic aldehydes with iodoarenes could be performed, in moderate yields however in most cases [Scheme^^62<xschr62>, Eq.^^(2)].[110]

Unfortunately, enolizable aldehydes were not tolerated with this procedure and mixtures of mono-, di- and tri- arylated aldehydes were obtained with several substrates. Moreover, and in sharp contrast with the previous procedure, the arylation was limited in this case to methyl groups as the arylation at a methylene position was found to be inefficient. Here again, a key dimeric intermediate could be isolated and characterized, this dimeric complex evolving to a monomeric palladium complex upon dissolution in deuterated acetic acid.

These pioneering studies set the stage for the development of alternative transient directing mediators and conditions that are summarized in Scheme^^63<schr63>. These mediators include 2-methoxyethylamine, a cheap and efficient mediator reported by the Bull group to promote the β-arylation of aldehydes with iodoarenes as well as an intramolecular version yielding indanes (Scheme^^63<xschr63>, a)[111] and L-valine, which was shown to be efficient for the chemoselective C($sp^3$)<C->H β-arylation of 2,2-alkylmethyl arylacetaldehydes with iodoarenes with good levels of efficiency, although with over-arylations in some cases (Scheme^^63<xschr63>, b).[112] In this case, the selectivity observed for the activation of the C($sp^3$)<C->H over the C($sp^2$)<C->H bonds was rationalized by the relative stabilities of the corresponding 5- and 6- membered ring palladium intermediates, respectively. Noteworthy, substituting L-valine for L-*tert*-leucine as the transient directing

mediator gave rise to a moderate but promising 40^% *ee*. The combination of a sterically demanding 3-amino-*N*-(*tert*-butyl)propenamide transient directing mediator and 5-(trifluoromethyl)pyridin-2-one as a ligand for palladium was found to efficiently promote the β,β'-diarylation of cyclohexanecarbaldehydes with iodoarenes (Scheme^^63<xschr63>, c).[113] In this case, and based on deuterium exchange experiments, the reaction mechanism was proposed to involve a transient enamine rather than an imine. A related aminoamide transient directing mediator, in the absence of an additional pyridine ligand, was finally reported by the Wei group in 2019 for the β-arylation of methyl groups in aliphatic aldehydes with iodoarenes (Scheme^^63<xschr63>, d).[114]

An important step forward for the direct arylation of aliphatic aldehydes has been achieved in 2020 by the group of Li and Ge who reported the γ-arylation of tertiary aldehydes with various iodoarenes, in moderate to good yields, where previous processes could only reach β-positions (Scheme^^64<schr64>).[115] The success of the method lies in the use of an α-aminoacid, namely L-phenylalanine to generate a fused 5,6-palladabicyle, in combination with a 2-pyridinone ligand that could act as an internal base accelerating the C($sp^3$)<C->H bond cleavage. Also, while γ-methyl groups were effectively activated, methylenes were again left untouched. As a note, since heteroaryl aldehydes were suitable reactants for the γ-arylation, the authors could further demonstrate the efficiency of their strategy by synthetizing a couple of triphenylamine-containing mechanofluorochromic materials, with a single extra step.

Logical further developments were next devoted to the extension of these processes to aliphatic ketones, which was actually pioneered by the group of Yu in 2016. Using reaction conditions similar to those they reported for the (hetero)arylation of *ortho*-methylbenzaldehydes, the authors could also perform the arylation of C($sp^3$)<C->H bonds in methyl groups at the β position in aliphatic ketones with iodoarenes and by simply using

glycine as the transient directing mediator [Scheme^^65<schr65>, Eq.^^(1)].[98] About a year later, the same group could extend their method to the β-arylation of methylene C($sp^3$)<C->H bonds in aliphatic ketones, using this time a β-aminoacid (3-amino-2-benzylpropanoic acid) as the transient directing mediator leading to the formation of a fused 5,6-membered palladabicycle instead of the 5,5-one formed with glycine, to deliver the corresponding arylated ketones in moderate to good yields [Scheme^^65<xschr65>, Eq.^^(2)].[116]

A variety of alternative conditions and transient directing mediators were next reported: these include β-alanine (Scheme^^66<schr66>, a),[117] its *N*-isopropylamide derivative (Scheme^^66<xschr66>, b)[114] and the corresponding α-aminoamide (Scheme^^66<xschr66>, c),[44] as well as a tridendate glycine dipeptide (Scheme^^66<xschr66>, d),[45] and, more recently, a dimethylacetamide substituted aliphatic oxime (Scheme^^66<xschr66>, e).[118] Also, the group of Yu reported recently an especially appealing enantioselective version of these processes, for the arylation of more specific substrates however, cyclobutylketones. In this process, the authors used D-valine along with 3-nitro-5-(trifluoromethyl)pyridinone as a ligand to obtain the corresponding optically enriched β-arylated cyclobutylketones in good yields and high levels of enantioselectivity (Scheme^^66<xschr66>, f).[119] Remarkably, the nature of the silver-based iodide scavenger was found to have a dramatic impact on the enantioselectivity as AgTFA and $Ag_3PO_4$ gave the opposite enantiomers, which was attributed, based on deuterium exchange experiments, to their different role in controlling the rate-limiting step. Eventually, the groups of Sorensen and Yu recently disclosed a palladium-catalyzed intramolecular version of a similar process, using glycine as the transient directing mediator and pyridinone ligands, enabling the intramolecular β-arylation of ketones bearing a remote iodoarene to indanes in high to excellent yields and high diastereoselectivity, accounted for a specific well-ordered and rigid Pd(II/IV) transition state (Scheme^^66<xschr66>, g).[120]

As for the mechanism of the C($sp^3$)<C->H (hetero)arylation of aliphatic aldehydes or ketones, the aforementioned processes using a transient imine directing group are believed to share the one depicted in Scheme^^61<xschr61>, starting with aliphatic aldehydes and ketones instead of aromatic ones.

After the disclosure of these pioneering reports, 2019 saw the emergence of several works in the field such as the dehydrogenative β-arylation of secondary aliphatic aldehydes with an excess of arenes using β-alanine as the transient directing mediator. The Wang group could indeed obtain a range of (*E*)-cinnamaldehydes in moderate yields (Scheme^^67<schr67>),[121] this process constituting a rare cross-dehydrogenative coupling employing potassium peroxodisulphate as the oxidant.

As evidenced with all examples overviewed in this section, the transient imine directing group strategy has proven to be quite efficient for the development of a range of innovative and attractive processes for the direct arylation of C($sp^3$)<C->H bonds in aldehydes and ketones. Some efforts have also been devoted to other types of transformations which will be discussed in the following sections, starting with alkylations and alkenylations.

#### 4.2.1.2. Alkylation and alkenylation reactions

In sharp contrast with arylation reactions of carbonyl derivatives, their alkylations and alkenylations have been much less investigated, despite a strong synthetic potential, and there are to date only a limited number of reports, only with ketones as starting materials, all published by the group of Dong. In this case, the authors took advantage of a transient directing enamine obtained by employing a secondary amine transient directing mediator, instead of an imine. The overall process does not therefore resemble an activation of a C($sp^3$)<C->H bond but actually involves the activation of a C($sp^2$)<C->H bond in the transient enamine. Based on their previous observation that 3-methylcyclopentane-1,2-dione could be efficiently ethylated with ethylene using Wilkinson's catalyst along with 2-aminopyridine as

the transient directing mediator,[122a] Mo and Dong reported in 2014 a remarkably efficient α-ethylation of a range of cyclopentanones under a high pressure of ethylene using a rhodium catalyst dimer along with catalytic amounts of a bifunctional pyrrolidinopyridine as the transient directing mediator in the presence of a N-heterocyclic carbene ligand (Scheme^^68<schr68>).[122b] While the regioselectivity can be explained by the selective formation of the less hindered enamine, the moderate diastereoselectivity can be accounted for a diastereoselective protonation at the less-hindered face, thus affording some diastereoselectivity. Interestingly, the reaction could be performed on a gram-scale and, to gain some insights into its mechanism, the authors isolated two key rhodacycles as both a dimer and a monomer.

Afterwards, the Dong group extended the scope of their reaction and fully exploit the potency of their remarkably efficient peculiar bifunctional transient directing mediator. They indeed showed that terminal alkenes could also be efficiently used to yield the corresponding branched alkylated cyclopentanones, by switching to iridium catalysis however [Scheme^^69<schr69>, Eq.^^(1)].[122c] The key iridacycle could here again be isolated. An intramolecular version, using rhodium or ruthenium catalysis along with 2-aminopyridine as the transient directing mediator could furthermore be developed,[122d] and interestingly, switching to optically pure BINAP gave a promising 74^% *ee*. Alkynes were also shown to be good reaction partners and afforded the corresponding *exo*-alkenylated cyclopentanones in good yields [Scheme^^69<xschr69>, Eq.^^(2)].[122e] This alkenylation could be extended to acyclic ketones using a hydrazinopyridine as the transient directing mediator and at the cost of an additional hydrogenation or hydration step, β-alkylated ketones could be obtained in moderate yields [Scheme^^69<xschr69>, Eq.^^(3)].[122f]

#### 4.2.1.3. Halogenation and C($sp^3$)<C->O bond formation

On top of all the C($sp^3$)<C->H bond functionalization reactions of aldehydes and ketones overviewed so far, and involving the formation of carbon-carbon bonds, some efforts have also been devoted to the development of processes for their direct heterofunctionalization, mostly halogenations and oxygenations. For instance, the group of Yu reported in 2018 an efficient enantioselective process for the fluorination of benzylic C<C->H bonds in *ortho*-alkylbenzaldehydes using the transient imine directing strategy with a chiral aminoacid-derived amide and palladium catalysis. Indeed, using a *N*-fluoro-2,4,6-trimethylpyridinium salt as the fluorinating agent in the presence catalytic amounts of homochiral L-*tert*-leucine diethylamide as the transient directing mediator and pentafluorobenzoic acid in benzene at 70^°C led to the formation of a range of fluorinated *ortho*-alkylbenzaldehydes in moderate yields and excellent enantiomeric excesses (Scheme^^70<schr70>).[123] The solvent was here crucial to avoid competing oxygenation, the use of acetic acid leading for instance to the corresponding acetoxylation. The authors could isolate and characterize by XRD a key fused 5,6-palladabicycle intermediate and the high levels of enantioselectivity were believed to result from the steric repulsion between the bulky transient directing group and the alkyl chain of the *ortho*-alkylbenzaldehydes.

In addition to fluorination, *ortho*-methylbenzaldehydes can be efficiently acetoxylated at their benzylic position as shown earlier this year by the group of Bao. In this process, acetylhydrazine was selected as the transient directing mediator of choice and acetic acid could be employed both as the solvent of the reaction and the source of the acetoxy group, in the presence of potassium peroxodisulfate oxidant, of which the lipophobicity could be overcome by the addition of a specific molecular sieve, to deliver the corresponding acetoxylated products in decent yields (Scheme^^71<schr71>).[124] A hydroxylation by the Yu group, which could extend the Schönecker's[125] and Baran's[126] copper-mediated C($sp^3$)<C->H aerobic oxidation to the use of transient directing groups for the site-selective

hydroxylation of pentacyclic triterpenoids in fair to excellent yields, was also reported recently.[127]

At this stage of this review article, the efficiency and synthetic usefulness of the transient imine directing group strategy for the directed functionalization of C($sp^3$)<C->H bonds in both aromatic and aliphatic aldehydes and ketones has been well documented. Over the years, a range of elegant, innovative, and useful processes has been developed based on this strategy that can actually be utilized the other way around, significantly expanding the substrate scope of these processes. Indeed, by using now an aldehyde as a transient directing mediator, aliphatic amines can be utilized as substrates and methods developed for their transiently directed functionalization will now be overviewed.

#### 4.2.2. C($sp^3$)<C->H bond functionalization of amines

The development of efficient and straightforward methods for the direct functionalization of aliphatic amines indeed constitutes a challenge of utmost importance due to both their use as key building blocks and their omnipresence in a plethora of natural products, biologically active substances as well as functional materials. While the development of transition-metal-catalysis has efficiently provided new synthetic tools for their synthesis, such as C<C->N cross-coupling reactions,[81] or hydroaminations of unsaturated substrates,[128] synthetic challenges still remain, and a highly efficient strategy that has emerged over the last five years relies on the transiently directed functionalization of C($sp^3$)<C->H bonds in aliphatic amines through the use of transition-metal catalysis, and more specifically palladium catalysis.[129] The transient formation of imines from the condensation of amine substrates with aldehydes or ketones used as transient directing mediators has proven to be remarkably efficient for the design and development of such processes that will be discussed in the following sections. As an important note for the reader who would be interested in using such reactions, attention should be paid to the exact nature

of the amine substrates utilized, their substitution patterns and the scope of the processes since specific substrates are quite often used to inhibit competing side reactions such as dehydrogenations.

#### 4.2.2.1. (Hetero)arylation reactions

Over the last few years, the major focus for the functionalization of C($sp^3$)<C->H bond in aliphatic amines has certainly been put on their γ-(hetero)arylation through the use of a transient imine directing group, a field that has been pioneered by the groups of Dong and Yu starting from 2016. While the former reported an efficient process based on the use of stoichiometric amounts of a transient aldehyde mediator, the latter could efficiently utilize it in catalytic amounts only. Indeed, to efficiently perform the arylation of aliphatic primary amines, Dong and coworkers took advantage of palladium catalysis along with the use of quinoline-8-carbaldehyde as the transient directing mediator. In this process, diaryliodonium salts, used in combination with a bulky, non-coordinating organic base (2,6-di-*tert*-butyl-4-methylpyridine, DTBMP) were shown to be the arylating agents of choice to deliver the desired products, by means of a benzoyl derivatization for more convenient purifications, in moderate to good yields [Scheme^^72<schr72>, Eq.^^(1)].[130] Unfortunately, the products were obtained as mixtures of mono- and di- arylated products on some occasions, somehow limiting the scope of the process. The authors could eventually use the transient directing mediator in catalytic amounts, with an erosion of the yield however.

Concomitantly, the group of Yu reported a different set of reaction conditions based on the use of catalytic amounts of 2-hydroxynicotinaldehyde as the transient directing mediator and iodoarenes as more convenient arylating agents. With these conditions, a broad range of γ-(hetero)arylated primary amines could be obtained, after Boc protection, in decent to excellent yields [Scheme^^72<xschr72>, Eq.^^(2)].[131] Apart from some issues with diarylation, methylene C($sp^3$)<C->H bonds could also be functionalized and substitution α to

the nitrogen atom was no longer mandatory. Interestingly, the transient directing group utilized by the Dong group only led to the formation of the arylated product in very poor yield under these reaction conditions. As a note, a very close process was recently reported by the groups of Kwak, Kim and Jung, by simply adding a bromine atom on the transient directing mediator.[132]

After the disclosure of these two pioneering reports, alternative processes and conditions with various levels of generality and efficiency have been reported. Indeed, the group of Murakami could demonstrate in 2017 the effectiveness of bulky salicylaldehydes as transient directing mediators for the γ-(hetero)arylation of aliphatic amines. Although used in stoichiometric amounts, 3,5-di-*tert*-butylsalicylaldehyde was shown to be the best transient directing mediator to deliver, under palladium(II) catalysis and after Boc derivatization, the corresponding arylated amines in moderate to good yields (Scheme^^73<schr73>, a).[133] Some biased methylene C($sp^3$)<C->H bonds could also be arylated, as well as 2-ethylaniline using in this case catalytic amounts of the transient directing mediator only. The same year, the group of Ge reported that simple glyoxylic acid monohydrate was also an efficient transient directing mediator for the γ-arylation of a range of aliphatic amines with both electron -rich and -poor iodoarenes (Scheme^^73<xschr73>, b).[134] Unfortunately, the position α to the nitrogen atom had to be disubstituted to favor the reaction through Thorpe-Ingold effect and avoid the potential dehydrogenation to the corresponding imine.

This γ-arylation could also be extended to free amino esters -- however with a subsequent reesterification -- (Scheme^^73<xschr73>, c)[50] and $\beta^2$- and $\beta^3$- amino esters (Scheme^^73<xschr73>, d)[135] using 2-hydroxynicotinaldehyde as the transient directing mediator, already used by Yu. Notably, acetals can be utilized instead of aldehydes as transient directing mediators, as highlighted by the Bull group which demonstrated the efficiency of phenoxy- and 4-(trifluorophenoxy)- acetaldehyde methyl acetals for the γ-

arylation of aliphatic amines in moderate yields (Scheme^^73<xschr73>, e).[136] In this case, addition of water was required to form the aldehyde transient directing mediator in^^situ.

As for the mechanism of the transformation, of which the stabilizing effect of the transient directing group has been demonstrated by computational studies,[137] it is believed that these processes share the one depicted in Scheme^^74<schr74>. It would first start with the condensation of the aliphatic amine onto the aldehyde to deliver the corresponding transient imine moiety that would further coordinate the palladium catalyst. $C(sp^3)$<C->H palladation would subsequently occur to generate a stable fused palladabicycle that would next undergo oxidative addition with the aryl halide (or diaryl iodonium salt) to yield the corresponding Pd(IV) intermediate. Further halogen abstraction with a silver salt would trigger the final reductive elimination, thereby delivering the arylated transient imine substrate. Eventually, hydrolysis would occur to afford the desired arylated amine (Scheme^^74<xschr74>).

Provided that an additional pyridinone ligand was utilized, the group of Yu used substituted benzaldehyde and phenyl-2-oxoacetic acid as efficient transient directing mediators, in catalytic amounts, to selectively perform both the γ- and δ- (hetero)arylation of aliphatic amines, respectively, the size of the palladacycles formed thus being successfully controlled [Scheme^^75<schr75>, Eqs.^^(1) and (2), resp.].[138] Indeed, while the combination of a 5-(trifluoromethyl)pyridinone ligand with 6-chloro-substituted hydroxybenzaldehyde transient directing mediator promoted the formation of a fused 5,6-palladabicycle and subsequent arylation at γ-position, the combination of a 5-nitropyridinone ligand with 2-(2-methoxyphenyl)-2-oxoacetic acid transient directing mediator enabled the formation of a fused 6,5-palladabicycle and thereby a challenging, broadly applicable, δ-(hetero)arylation of aliphatic amines with (hetero)iodoarenes in decent to high yields.

As demonstrated with all the examples overviewed in this section, the transient imine directing strategy has proven to be rather efficient for the development of a range of innovative and attractive processes for the directed arylation of C($sp^3$)<C->H bonds in aliphatic amines. Although no other report dealt with C($sp^3$)<C->C bond formations, some efforts have been devoted to halogenations and C($sp^3$)<C->O bonds formation which will be discussed in the following section.

#### 4.2.2.2. Halogenation and C($sp^3$)<C->O bond formation

Little efforts have been devoted to date to address both the fluorination and the oxygenation of C($sp^3$)<C->H bonds in aliphatic amines. In this context, the group of Yu reported earlier this year the palladium-catalyzed γ-fluorination of aliphatic amines relying on the use of 2-hydroxynicotinaldehyde as an efficient transient directing mediator enabling the C<C->H bond palladation of both $CH_3$ and $CH_2$ groups under two different sets of conditions (Scheme^^76<schr76>).[139] While NFSI enabled the methylene γ-fluorination of aliphatic amines [Scheme^^76<xschr76>, Eq.^^(1)], 1-fluoro-2,4,6-methylpyridinium tetrafluoroborate was preferred as the fluorinating agent for methyl groups (Scheme^^76<xschr76>, Eq.^^(2)]. For both procedures, a pyridinone ligand, 3-nitro-5-chloropyridinone and 3-bromo-5-(trifluoromethyl)pyridinone, respectively, enabled a significant improvement in terms of efficiency. While the presence of silver salts was crucial for fluorination at methylene positions, it was found to proceed smoothly in their absence for the fluorination of methyl groups. As for the mechanism associated to this fluorination, it would follow, according to DFT studies, the catalytic cycle depicted in Scheme^^76<xschr76> for the methylene fluorination. It would start with the formation of the transient imine moiety which would coordinate, along with one additional molecule of the transient directing mediator acting in this case also as a pyridinone ligand, the palladium catalyst to generate a first palladacycle. C<C->H activation would subsequently occur to furnish a second fused 5,6-palladabicycle

that would then undergo a ligand exchange. The approach of the fluorinating agent upon silver assistance would further afford the optimal substrate for the following bimetallic oxidative addition step. The latter would indeed enable the formation of the corresponding fused palladium(IV) 5,6-metallbiacycle, which would further undergo reductive elimination to afford the Pd(II)-coordinated fluorinated transient imine product prior to be decoordinated upon action of acetic acid, thereby regenerating the initial palladium catalyst as well as delivering the Pd-free imine product. Imine hydrolysis would eventually occur to yield the desired fluorinated amine. As for the C<C->H fluorination of methyl groups, computational studies suggested that the main catalytic steps were identical, apart from the fluoropyridinium salt oxidative addition which would be direct and not bimetallic.

The same year, two different reports dealing with C($sp^3$)<C->H bonds oxidation in aliphatic amines were disclosed: the first one, reported by the group of Hartwig, on the β-C($sp^3$)<C->H bond acetoxylations in α,α'-disubstituted amines, and the second one, reported by the groups of Sunoj and Yu, on both the γ-C($sp^3$)<C->H bond acyloxylations and alkoxylations. In the first case, the β-C($sp^3$)<C->H acetoxylation of a range of primary alkylamines with (diacetoxyiodo)benzene using palladium catalysis along with salicylaldehyde as the transient directing mediator in the presence of a mono-protected aminoacid ligand was shown to occur in moderate to good yields [Scheme^^77<schr77>, Eq.^^(1)].[140] While two key substrate coordinated palladium complexes could be isolated, DFT calculations suggested that the reaction would be likely to involve a rare 4,6-palladacbiycle, unfortunately not isolable.

A similar but complementary oxygenation of the γ-position of alkylamines was reported by the Sunoj and Yu groups the same year. In their process, palladium catalysis in combination with 2-hydroxynicotinaldehyde as the transient directing mediator in the presence of 1-fluoro-2,4,6-methylpyridinium tetrafluoroborate oxidant was found to

efficiently oxidize γ-C($sp^3$)<C->H bonds in alkylamines with either carboxylic acids or alcohols, in good to excellent yields [Scheme^^77<xschr77>, Eqs.^^(2) and (3), resp.].[141] Notably, no fluorination of the substrates was observed.

These three last examples further showcase the efficiency of the transient imine directing group strategy for the functionalization of C<C->H bonds, a strategy that has enabled the development of efficient and straightforward processes for the directed functionalization of aldehydes, ketones as well as amines. This strategy is not limited however to C<C->H bond functionalization and was actually also proven to be especially useful for the less-known but highly efficient and appealing activation of C($sp^2$)<C->C bonds in ketones, which will be at the core of the next section.

**4.3. C($sp^2$)<C->C($sp^3$) bond functionalization**

The activation of C<C->C bonds using imine transient directing groups has first been explored and pioneered by the group of Jun. Indeed, in 1999, they could already observe the cleavage of such bonds in imines upon treatment with a rhodium(I) catalyst. In this process, a methylketone was reacted with an unactivated terminal alkene in the presence of Wilkinson's catalyst along with 2-amino-3-picoline as the transient directing mediator to afford, at high temperatures, the methylketone bearing the corresponding new side-chain resulting from the incorporation of the alkene, used in excess to drive the equilibrium (Scheme^^78<schr78>).[142a] The mechanism of the reaction was thus proposed to proceed through the pathways already depicted in Scheme^^10<xschr10> for the classical alkylation of aldehydes with unactivated alkenes under the same reaction conditions. Hence, it has been presumed to start with the condensation of 2-aminopicoline onto the ketone substrate to furnish a transient imine moiety that would further coordinate the rhodium catalyst. Subsequently, C<C->C activation via oxidative addition would occur to generate the corresponding rhodacycle that would undergo β-hydride elimination to afford a rhodium

hydride intermediate, which would further be migratory inserted into the unactivated terminal olefin. Reductive elimination would subsequently occur to regenerate the rhodium catalyst and deliver the new imine whose hydrolysis would eventually release both the 2-aminopicoline transient directing mediator and the new ketone. Thereafter, the group of Jun could extend the process to transimination with cyclohexylamine,[142b] but also to aliphatic alcohols[142c] and amines[36c] upon in^^situ oxidation with olefins under rhodium catalysis or even to allylic alcohols[35b] through in^^situ Rh-catalyzed isomerization followed by alkylation of the resulting aldehyde, as discussed in section 4.1.1.

Some 15^^years later, and using slight modifications of the reaction conditions, the group of Dong reported an intramolecular version of this reaction starting from cyclobutanones bearing an unsaturated side-chain at the 3 position yielding a range of fused bicyclic ketones formed in moderate to high yields [Scheme^^79<schr79>, Eq.^^(1)].[143a] The mechanism of the transformation was proposed to start with the formation of the imine followed by oxidative addition of the rhodium(I) catalyst into the cyclobutanone C<C->C bond to deliver the corresponding fused 5,5-membered rhodium(III) bicycle that would further coordinate the remote alkene. 1,2-Migratory insertion followed by reductive elimination would subsequently occur to afford the corresponding bicyclic imine product. Hydrolysis would eventually release both the transient auxiliary and the desired product. Next, the Dong group extended this approach to the cyclization of acyclic unsaturated ketones [Scheme^^79<xschr79>, Eq.^^(2)][143b] and to the homologation of benzocyclopentan-1-ones to benzocycloheptan-7-ones with ethylene [Scheme^^79<xschr79>, Eq.^^(3)].[143c] Remarkably, the same group could recently demonstrate the efficiency of this strategy by applying it to an elegant enantioselective total synthesis of penicibilaenes.[144]

Back in 2016, the same group could even push the concept one step further by trapping the intermediate rhodacycle resulting from the activation of cyclic ketones, not with

an internal remote alkene but with an internal aromatic ring through C($sp^2$)<C->H activation. Remarkably, depending on the ring size of the starting ketone, the C<C->C bond activation occurred either at the proximal or the distal bond. Indeed, while 3-aryl-cyclopentanones led to ring expansion to benzocyclohexan-1-ones, switching to 3-aryl-cyclohexanones resulted in a ring contraction to the corresponding indanones, both in moderate to good yields [Scheme^^80<schr80>, Eqs.^^(1) and (2)].[145a] When starting from ring-fused 3-aryl-cyclopentanones, spiroindanones could be obtained in moderate to high yields, further highlighting the remarkable efficiency and versatility of these processes [Scheme^^80<xschr80>, Eq.^^(3)].[145b] The selectivity towards the distal C<C->C bond activation with respect to the aryl group was attributed in this case to the steric hindrance generated by the bulky IPr NHC ligand.

In addition to alkenes and arenes, arylboronates were also shown to be efficient coupling partners, affording an efficient entry to arylketones from readily available starting materials. Though the proximal/distal C<C->C bond activation selectivity on substituted cyclopentanones was here less effective, the authors could perform the reaction on a very broad range of substrates with moderate yields (Scheme^^81<schr81>).[145c]

C<C->C bonds could also be activated using an isothiocyanate-based transient directing group for carbonylative transformations, as demonstrated by the Bower group. In this process, a range of aminocyclopropanes could indeed be reacted with cyclohexyl isothiocyanate to furnish the corresponding transient thiourea directing group able to promote the carbonylative C<C->C bond activation of the cyclopropane core by a rhodium(I) catalyst yielding the corresponding γ-lactams. Thus, in a one-pot procedure, *N*-cyclopropylamine could be converted into *N*-benzyl-γ-butyrolactam in 70^% yield [Scheme^^82<schr82>, Eq.^^(1)].[146] Also using a one-pot procedure with an isocyanate in place of an isothiocyanate, cascade polycyclizations could be triggered starting from a range of

cyclopropylamines bearing a remote alkyne moiety to be inserted after carbonylative C<C->C bond activation with high efficiency [Scheme^^82<xschr82>, Eq.^^(2)].

As overviewed with all examples collected in this section, imines are definitely among the most useful and widely used transient directing groups and have been recently utilized for the development of an impressive array of transformations that typically proceed with exquisite levels of selectivity. They indeed enabled the design of remarkably efficient and useful processes for the functionalization of a wide range of C<C->H and C<C->C bonds and there is no doubt that other processes based on the use of transient imines directing groups will be reported in the near future, for the functionalization of other substrates and other bonds and for the design of novel enantioselective processes. In this perspective, the recently reported direct arylation of B<C->H bonds in carboranes[147] and asymmetric reductive Heck hydroarylation of alkenes are quite illustrative.[148]

Next in class are carboxylic acids and carbamates whose usefulness as transient directing groups has also been recently highlighted, notably to efficiently promote the arylation and olefination of phenols, fluoroarenes and amines using palladium catalysis. The use of carbon dioxide as a transient directing mediator enabling the intermediate installation of carboxylic acids and carbamates as traceless transient directing groups will therefore be reviewed in the following section.

## 5. Transient Carboxylic Acid- and Carbamate-Directed Transformations

If carbon dioxide constitutes an attractive C1 building block whose chemistry boomed recently, it also constitutes an excellent reagent for the temporary installation of transient directing groups, readily cleaved after playing its role. In this perspective, the Young group elegantly implemented the well-known carbonatation of amines, which utilizes carbon dioxide to form a transient carbamate in^^situ for the directed γ-C($sp^3$)<C->H arylation of primary and secondary amines. Remarkably, dry ice was directly employed to build a suitable pressure

of $CO_2$ and enabled the transformation to proceed through the transient formation of the corresponding carbamate moiety and its further palladium-catalyzed arylation with iodoarenes, affording a range of γ-arylated amines in moderate to good yields, provided that the starting amines have at least one substituent at their α-position, most certainly to avoid dehydrogenation or provide some conformational rigidity [Scheme^^83<schr83>, Eq.^^(1)].[149a] This process was later on extended by the same group to the C($sp^2$)<C->H arylation of both primary and secondary benzylamines, affording the corresponding mono- or di- arylated desired products in good to high yields [Scheme^^83<xschr83>, Eq.^^(2)].[149b] Worth to be highlighted, all steps in these processes could occur in one pot without further manipulation.

If amines are convenient substrates for the installation of a transient directing carbamate since they readily react with carbon dioxide, the same holds true for phenols and arenes, whose carboxylation is well-known to generate benzoic acids. Since reports based on such a carboxylation for the in^^situ generation of benzoic acids and their use in directed C<C->H functionalization reactions are still based on sequential one-pot procedures, they are not therefore strictly “transiently directed” but still deserve to be briefly overviewed due to their novelty and the possibilities offered by benzoic acids as “traceless” directing groups. This was elegantly implemented by the Larrosa group as soon as 2014 with a remarkable *meta*-C($sp^2$)<C->H arylation of phenols relying on a transient *ortho*-carboxylation. In this process, phenols are indeed treated with potassium hydroxide under 25^^atm of $CO_2$ to afford the Kolbe-Schmidt carboxylation product prior to be subjected to a Pd(II)/Pd(IV) C<C->H arylation and further in^^situ decarboxylation in the presence of PEPPSI-IPr catalyst or $Pd(OAc)_2$. With these conditions, a range of phenols could be efficiently *meta*-arylated with various iodoarenes in moderate to good yields [Scheme^^84<schr84>, Eq.^^(1)].[150a] Later on, in 2018, the same group could extend their process to other types of arenes, at the cost of a harsher pre-carboxylation relying on a directed *ortho*-metalation with *sec*-BuLi. The *meta*-

arylation could subsequently take place with a range of iodoarenes using the more classical $Pd(OAc)_2$ catalyst to deliver the corresponding arylated arenes in moderate to good yields [Scheme^^84<xschr84>, Eq.^^(2)].[150b] Interestingly, the authors could extend the scope of the reaction to a range of (trifluoro)methoxybenzenes with electron-rich iodoarenes. Eventually, Larrosa and coworkers efficiently extended this process in 2020 to the *meta*-alkenylation of similar substrates with various alkynes. By substituting palladium for ruthenium catalysis, the authors could indeed deliver a range of *meta*-alkenylated fluoroarenes in moderate to good yields [Scheme^^84<xschr84>, Eq.^^(3)].[150c]

As evidenced by the recent examples overviewed in this section, carbon dioxide is emerging as an inexpensive and efficient transient directing mediator for both $C(sp^2)$<C->H and $C(sp^3)$<C->H bonds functionalization reactions relying on intermediate carboxylations to benzoic or carbamic acids that efficiently coordinate to a palladium catalyst. As with other transient directing groups, it relies on the reversible covalent installation of a transient directing group coordinating the metal complex that performs the actual C<C->H activation. However this is not the only option available for a transient directing group to be operative. Another challenging approach, although remarkably elegant and efficient, has been indeed recently explored relying on non-covalent interactions, mostly electrostatic ones as well hydrogen bonds and coordinate bonds (donor-acceptor). These will be discussed in the following section.

## 6. Transformations Mediated by Non-Covalent Interactions

Over the last decades, remarkable and pioneering studies have been conducted to explore the possibility to use a transient auxiliary bonded to the substrate simply by weak, non-covalent interactions such as electrostatic interactions, hydrogen and coordinate bonds (donor-acceptor).[151] If the transient directing mediators used in these processes can be seen as ligands for the metal center, their coordination to the substrate still enables its activation,

often allowing to overcome its innate reactivity, which usually cannot be achieved with more classical transient directing groups. Furthermore, non-covalently directed transformations were in most cases proven to exhibit high levels of enantioselectivity in the presence of chiral transient directing mediators. The following sections will thereby focus on the use of transient directing mediators that are bonded to the substrate by non-covalent interactions. Supramolecular catalysts acting as biomimetic enzymes through substrate immobilization to achieve peculiar oxidation or hydrogenation transformations without leading to an actual insertion of the metallic center into the bond to be activated and systems that involve extrusion or modification of the substrate functional group utilized to attach the transient directing group therefore stand outside the scope of this review article. Still, some enantioselective hydrogenations could be seen as transiently directed reactions involving non-covalent interactions[152] but will not be covered for the sake of conciseness.

**6.1. Electrostatic interactions**

As it comes to non-covalent interactions, one of the first ones that comes to mind is the electrostatic interaction, which has been nicely implemented in the transient directing group strategy over the last decade. Numerous transient directing mediators electrostatically bonded to their substrates have been indeed reported to efficiently promote transformations such as hydroformylations, cycloadditions, selective C<C->H borylations or cross-coupling reactions. This approach entails the main advantage of enabling high control over the site-selectivity in the transformation, mostly due to the large size of the directing groups that can be easily modulated. This approach has been pioneered by the Breit group which reported in 2008 an efficient hydroformylation of unsaturated carboxylic acids by designing a range of hybrid ligands bearing both a triarylphosphine coordinated to the rhodium catalyst as well as a guanidine electrostatically anchoring the initial carboxylic acid through acid-base and additional hydrogen bonding interactions (see section 6.2). Using this approach along with a

$CO/H_2$ gas mixture, they could hydroformylate unsaturated acids with high levels of regioselectivity, dictated by the transient directing group, and in moderate to good yields [Scheme^^85<schr85>, Eq.^^(1)].[153a,b]

This approach was next extended to acrylic acids whose regioselective hydroformylation was followed by a spontaneous decarboxylation yielding either the corresponding aldehydes [Scheme^^85<xschr85>, Eq.^^(2)],[153c] or alcohols resulting from a subsequent reduction of the aldehyde when the reaction was performed at a higher temperature [Scheme^^85<xschr85>, Eq.^^(3)].[153d] When starting from β,γ-alkynoic acids, their hydroformylation and subsequent double bond hydrogenation provided the corresponding saturated oxo-carboxylic acids.[153e] Starting from propiolic acids, the Breit group developed an efficient entry to functionalized aldehydes resulting from the trapping of the intermediate 2-formyl-α,β-unsaturated carboxylic acids with a range of nucleophiles such as electron-rich arenes or indoles prior to an in^^situ decarboxylation [Scheme^^85<xschr85>, Eq.^^(4)].[153f] The same group could take advantage of this type of transient directing mediators to perform similar transformations starting from alkenes and aldehydes in place of carboxylic acids, though the connection with the substrates rather occurred through hydrogen bonding than electrostatic interactions in these cases.[153g,h]

In a series of articles published between 2016 and 2019, the Phipps group reported other electrostatically directed transformations with exquisite levels of site-selectivity. Indeed, they could extend Hartwig's iridium-catalyzed borylation[154] to the selective *meta*-borylation of quaternary ammonium salts derived from aryl-, (hetero)arylmethyl-, -ethyl- and -propyl-amines as well as phosphonium salts based on the use of a modified bipyridine ligand bearing a distal sulfonate electrostatically interacting with the ammonium or phosphonium ions embedded in the substrate and therefore directing the iridium catalyst bound to the bipyridine moiety towards the targeted *meta*-$C(sp^2)$<C->H bond [Scheme^^86<schr86>, Eq.^^(1)].[**155**]

In a follow-up report, the authors could further highlight that the process was not limited to positively charged substrates since benzylamine-, phenethylamine-, and phenylpropylamine-derived amides could also be *meta*-selectively borylated based on hydrogen bonding between the amide proton and the sulfonate of the transient directing mediator in excellent yields and levels of site-selectivity [Scheme^^86<xschr86>, Eq.^^(2)].[156] This approach elegantly enabled to overcome the innate reactivity of the substrates, mostly based on steric parameters, and broadened the scope of substrates amenable to Hartwig's borylation, provided however that, in most cases, the aromatic moiety was *ortho*-substituted to reach excellent yields.

The same group even pushed the process one step further with an enantioselective version of their method relying on the use of a dihydroquinine-derived chiral counterion. The authors could indeed report the desymmetrizing *meta*-selective borylation (and subsequent oxidation) of prochiral substrates at room temperature in high yields, decent to excellent site-selectivity and moderate to high enantioselectivity (Scheme^^87<schr87>).[157] The enantioselectivity control was here accounted for the steric clash implemented in the substrate attachment to the transient directing mediator through electrostatic interactions.

A similar approach for a really close synthetic transformation has actually also been developed by the group of Chattopadhyay for the *para*-selective borylation of (hetero) aromatic esters. In this process, reported in 2017, the authors opted for the potassium salt of a quinolin-2-ol-substituted bipyridine as the transient directing mediator to be electrostatically bonded to the ester group of the substrate. Provided, in most cases at least, that *ortho*-substituted substrates were utilized, excellent levels of *para*-selectivity could be obtained for the borylation of a broad range of (hetero)aromatic esters under similar reaction conditions [Scheme^^88<schr88>, Eq.^^(1)].[158a] About a year later, Chattopadhyay and coworkers could extend their process to the *meta*-selective borylation of (hetero)aromatic amides under the same reaction conditions. The connection between the cation and the amide moiety was

here believed to involve either an O<C->K or a π-K non-covalent interaction and a broad range of (hetero)aromatic amides could be *meta*-borylated in high yields and excellent levels of selectivity [Scheme^^88<xschr88>, Eq.^^(2)].[158b]

As demonstrated by the groups of Maleczka, Singleton and Smith, selective *ortho*-borylation could also be achieved by taking advantage of electrostatic interactions. Indeed, upon in^^situ transformation of phenols to the corresponding boronate esters, a classical Ir/dtbpy borylation could selectively be *ortho*-directed, via electrostatic interactions between the partially positively charged bipyridine ligand and the partially negatively charged OBPin protecting group (Scheme^^89<schr89>).[159] A range of *ortho*-borylated phenols were thereby obtained in good yields and excellent selectivity, which could further be rationalized by the calculation of electrostatic potential surfaces. More recently, the Chattopadhyay group could efficiently extend this strategy relying on electrostatic interactions between neutral ligand and substrates to the *meta*-selective borylation of anilides and *N*-arylsulfonamides.[160]

Electrostatic interactions could also be utilized to control the site-selectivity in palladium-catalyzed cross-couplings between aryldichlorides bearing a trifluoromethanesulfonamide moiety and a range of nucleophiles such as boronic acids, terminal alkynes, or anilines, as demonstrated by the Phipps group. Using Buchwald's sSPhos and s($^t$BuSPhos), whose sodium sulfonates can engage in electrostatic interactions with the sulfonamide anion in the substrates, the chloride at the *meta* position of the aryldichloride substrates could be selectively activated, in moderate to excellent yields [Scheme^^90<schr90>, Eq.^^(1)].[161a] Interestingly, the trifluoromethanesulfonamide moiety could also be substituted for a carboxylic acid or a sodium sulfonate in Suzuki-Miyaura-type cross-coupling reactions, affording the corresponding arylated products in moderate yields and excellent levels of *meta*-selectivity. Earlier this year, the same group could extend the process to cross-couplings with fluorinated (hetero)arenes, thus demonstrating that

electrostatically-directed palladium catalysis is also amenable to C<C->H activation [Scheme^^90<xschr90>, Eq.^^(2)].[161b] Sulfonamides, sulfamates, sulfonates, phosphonates and carboxylic acids were shown to be suitable groups that could be embedded in the starting arene, ensuring the involvement of the key electrostatic interaction. Recently, the authors could even push the concept one step further by assessing the size of the cation ($Li^+$, $Na^+$, $K^+$, $Rb^+$, $Cs^+$) electrostatically linking the substrate to the appropriate sulfonated phosphine transient-directing mediator to site-selectively perform Suzuki-Miyaura and Buchwald-Hartwig couplings on protected *ortho*,*meta*,*para*-di- to tri- chlorobenzylamines -- the bigger the cation, the further the activation.[161c]

A different but still related concept has also been studied and implemented in similar synthetic transformations, taking advantage of hydrogen bonds instead of electrostatic interactions. This is at the core of the following section.

**6.2. Hydrogen bonds**

Hydrogen bonding has indeed turned out to be as efficient as electrostatic interactions to attach a transient directing mediator to its substrate, especially for site-selective borylation processes. Indeed, as from 2012, Singleton, Maleczka, Smith and coworkers could report the *ortho*-borylation of Boc-protected anilines under classical Ir/dtbpy conditions. By taking advantage of hydrogen bonding between the aniline's proton and an oxygen atom of a pinacolate bound to iridium, the *ortho*-borylation of a range of anilines could be successfully performed in moderate to excellent yields (Scheme^^91<schr91>, a).[162a] Boc-protection is not mandatory since in^^situ BPin- or Beg- protected anilines were also shown to be viable substrates (Scheme^^91<xschr91>, b and c).[162b,c]

In a similar vein, Yamanaka, Kuninobu and coworkers could perform the *ortho*-selective borylation of aromatic thioethers, the hydrogen bonding involving a hydrogen atom α to the thioether and an oxygen atom of a pinacolate ligand. Under iridium catalysis with a

phenylbipyridine ligand, a broad range of aromatic thioethers could thus be selectively borylated in high yields and excellent selectivity (Scheme^^92<schr92>).[163]

While these methods involve hydrogen bonding with a hydrogen atom of the substrate, this is not strictly mandatory with proper ligand design. This was actually featured in an interesting example reported in 2015 by the group of Kuninobu and Kanai that relied on the use of a urea-bipyridine bifunctional ligand for *meta*-selective borylation transformations. In this system, the urea ensures hydrogen bonding with the substrate while the bipyridine, placed at the right position, coordinates to iridium, bringing it in close proximity to the *meta*-C<C->H bond that is thus selectively activated. This elegantly designed system enabled to selectively borylate a broad range of aromatic amides and phosphine oxides in moderate to excellent yields and levels of selectivity (Scheme^^93<schr93>).[164a] On top of exhibiting excellent levels of selectivity, this type of transient directing groups was in addition shown to significantly accelerate the reaction as well as showing high functional group recognition.[164b] and further one-pot direct derivatization of the boronate ester was shown to be possible.[164c]

Inspired by these results, the Sawamura group pushed this strategy one step further with the addition of a chiral BINOL-based monophosphite ligand to promote, using a similar urea-based transient directing mediator, the asymmetric iridium-catalyzed γ-C<C->H borylation and subsequent oxidation of a broad range of aliphatic amides and esters in high yields and enantioselectivity (Scheme^^94<schr94>).[165]

As a final note for this section, the groups of He and Zhang recently elegantly extended the use of these urea-based transient directing mediators to the enantioselective alkynylation of PMB-protected isatins under silver catalysis using chiral urea-based transient directing mediators.[166]

Another strategy taking advantage of weak interactions between the substrate and the transient directing mediator relying on coordinate bonds has been explored in the recent years and will be discussed in the following section.

**6.3. Coordinate bonds**

Coordinate bonds indeed also provide an efficient mean to reversibly install a transient directing group to a substrate. To date, the methods utilizing such strategies to site-selectively functionalize various scaffolds are taking advantage of either transition-metal-heterocyclic nitrogen coordinate bonds or the formation of Lewis acid-base adducts. The former has been pioneered by the group of Yu in 2017 through the design of templates able to form stable copper or palladium complexes, thus offering a strong and efficient anchor point for any nitrogen-containing heterocyclic substrate. Through the design of such bifunctional templates bearing additional coordinating groups, the group of Yu could indeed perform the remote C($sp^2$)<C->H alkenylation of a range of arylpyridines [Scheme^^95<schr95>, Eq.^^(1)] and quinolines [Scheme^^95<xschr95>, Eq.^^(2)] with activated olefins with almost surgical levels of site-selectivity at positions otherwise difficult to functionalize.[167a]

In a series of articles, and inspired by this work, the group of Maiti reported different templates for the same synthetic purpose using similar conditions,[167b] and further extended the process to thiazoles[167c] and to the alkylation of quinolines and various nitrogen-containing fused heterocycles.[167d] Eventually, the groups of Houk and Yu elegantly combined this strategy with the use of functionalized norbornenes to achieve the arylation of quinoline and isoquinoline derivatives at one C($sp^2$)<C->H bond further than in their previously developed process (see section 7.1).[167e]

Although indisputably efficient, this elegant strategy suffers from severe limitations such as the use of stoichiometric amounts of transition-metals in some cases as well as the complexity and molecular weight of the template *versus* the substrate that can limit the

attractiveness of the processes, especially in terms of sustainability. Yet, overcoming these limitations, coordinate bonds have also been utilized to perform the iridium-catalyzed borylation of different substrates such as aryl sulfides, pyridines, imidazoles and aromatic amides by the groups of Kuninobu, Kanai, Gramage-Doria and Nakao, relying on Lewis acid-base interaction with a bidentate iridium ligand bearing a boronate ester [Scheme^^96<schr96>, Eq.^^(1)],[168] a dialkylborane [Scheme^^96<xschr96>, Eq.^^(2)],[169] a zinc(II)-porphyrin moiety [Scheme^^96<xschr96>, Eq.^^(3)],[170] or an aluminum-biphenoxide [Scheme^^96<xschr96>, Eq.^^(4)],[169] respectively. Noteworthy, the group of Nakao recently implemented a similar strategy using a rhodium-aluminum complex to the C2-selective silylation of pyridines.[171]

A similar strategy, taking advantage of a ligand combined with a trialkylaluminum species, could be implemented by the groups of Xu, Luan and Ye to the double C<C->H annulation of enamides with alkynes towards 2-pyridones [Scheme^^97<schr97>, Eq.^^(1)],[172a] and their subsequent C3-selective post-alkenylation with similar reagents [Scheme^^97<xschr97>, Eq.^^(2)].[172b] In these processes, a phosphite ligand is used in combination with a bulky trialkylaluminum species to in^^situ form a transient coordinating directing group able to promote, under nickel catalysis, a range of C<C->H bonds alkenylations with alkynes in excellent yields.

While all the previously discussed strategies employing a transient directing group relied on reversible bondings or weak interactions with the substrate, a simple transient directing mediator, namely norbornene, has also been extensively revisited and studied over the last decade to achieve various efficient and straightforward transformations in combination with palladium catalysis based on innovative modifications of the venerable Catellani reaction. Processes based on this strategy will be reviewed in the following section.

**7. Norbornene-Mediated Transformations**

Discovered in 1997, the Catellani reaction, named after the Italian chemist Marta Catellani, is a remarkably powerful synthetic tool to simultaneously install two substituents on an arene from simple aryl halides.[173] This reaction relies on the use of a simple transient mediator, norbornene (NBE), that can cooperatively be used along with palladium catalysis for the concomitant *ipso*- and *ortho*- functionalizations of aryl halides with nucleophiles and electrophiles, respectively, through sequential C($sp^2$)<C->X/C($sp^2$)<C->H bonds activation (Scheme^^98<schr98>).[10]

This remarkable transformation has been extensively investigated recently and its combination with a directing group strategy has resulted in the design and development of innovative processes for the selective functionalization of C($sp^2$)<C->H bonds in arenes that will be overviewed in this section. Since in most cases an *ipso* functionalization of the C<C->X bond occurs, acting as the anchoring point, these reactions do not correspond to the definition of a transient directing group selected for the scope of this review article in which the initial binding site of the substrate must be recovered untouched after functionalization: they will therefore not be covered in this section and the same holds true for all processes in which the norbornene derivatives are incorporated in the product. This section will thus focus first on the *meta*- and *para*- selective functionalization of arenes bearing a directing or native functional group that enables the activation of the corresponding positions by the mean of a norbornene transient directing mediator. In the former case a classical directing group and transient directing group are actually combined which is borderline with respect to the scope of this review but still included since remarkable developments have been reported based on the Catellani reaction. While the norbornene can theoretically be used catalytically, most studies reveal that more than one equivalent is required.

### 7.1. Norbornene-mediated *meta*- and *para*-functionalization of arenes

To highlight the differences between such processes and the classical Catellani reaction, a simplified general mechanism explaining the *meta*-selectivity, observed in almost all cases, is depicted in Scheme^^99<schr99>. First, a directed *ortho*-C($sp^2$)<C->H activation of a Pd(II) catalyst occurs to generate a palladacycle able to coordinate the norbornene transient mediator which further undergoes a 1,2-migratory insertion to afford the corresponding Pd(II) intermediate. Subsequently, a second C($sp^2$)<C->H activation event takes place at the *meta* position to deliver the aryl-norbornyl-palladacycle prior to its oxidative addition with the coupling partner, leading to the corresponding norbornene-containing fused Pd(IV) bicycle. Upon reductive elimination, providing the *meta*-functionalization, and subsequent β-carbon elimination, extruding the norbornene mediator, the corresponding *meta*-functionalized *ortho*-palladated intermediate is obtained. Protonolysis eventually restores the *ortho* C<C->H bond, delivering the desired *meta*-functionalized arene and regenerating the Pd(II) catalyst.

Inspired by the seminal work of the Catellani group, and based on the aforementioned strategy, the Yu group first disclosed in 2015 the *meta*-selective alkylation and arylation of phenylacetamides bearing a fluorinated arylamide as the directing group. Through thorough ligand design, a tricyclic pyridine could be identified as an efficient ligand for this reaction that in addition limited the formation of the undesired norbornene-containing benzocyclobutene byproduct. This ligand enabled both the *meta* -alkylation and -arylation of a range of secondary phenylacetamides with alkyl or aryl halides through Pd(II)/norbornene cooperative catalysis in moderate to excellent yields, the main limitation being the restriction of the alkyl halide scope to iodomethane, ethyl 2-iodoacetate and benzyl iodides (Scheme^^100<schr100>, a).[174] The same year, the scope of their process was extended to less reactive alkyl iodides by switching to a modified norbornene mediator bearing a methyl ester at the C2 position, accelerating the migratory insertion of the arylpalladium species with norbornene (Scheme^^100<xschr100>, b).[175]

Concomitantly, the group of Dong reported a similar method starting from *N*,*N*-dialkylbenzylamines. In this process, triphenylarsine was found to be the best ligand for palladium along with a so-called rather complex “acetate cocktail” to promote the *meta*-selective arylation of the substrates in moderate to good yields (Scheme^^101<schr101>).[176] Unfortunately, this process suffers from severe limitations including a narrow scope, competing diarylation and the use of five different acetates in rather large amounts.

Based on these seminal reports, other nitrogen-containing directing groups were evaluated and a range of heterocycles were reported to promote such *meta*-selective functionalizations under palladium/norbornene cooperative catalysis. The group of Yu indeed reported a broadly applicable *meta*-selective (hetero)arylation of a wide range of anilines, phenols and related substrates equipped with proper directing groups in the presence of 3-acetamide-pyridine-2-ol ligands in high to excellent yields (Scheme^^102<schr102>).[177]

Inspired by these results, a rather impressive series of articles published between 2016 and 2020 followed on the *meta*-selective (hetero)arylation, and occasionally alkylation, of a plethora of substrates either bearing similar directing groups or featuring an innate coordinating functional group. The substrates for this transformation have been collected in Scheme^^103<schr103> and include (homo)benzylamines,[178--181] biarylamines,[181,182] arylacetic acids,[183] benzylsulfonamides,[184] benzylic alcohol acetal,[185] or 2-arylethylpyridines.[186]

In 2019 and 2020, the Yu group elegantly pushed the system one step further by demonstrating that the process actually does not require any pre-installed directing group when starting from either (fluoro)arenes [Scheme^^104<schr104>, Eq.^^(1)][187] or electron-rich alkoxyarenes [Scheme^^104<xschr104>, Eq.^^(2)].[188] In this case, the innate reactivity providing the initial C<C->H activation *ortho* or *para* to the functional group is relied on.

Asymmetric variants were quick to follow, starting from rather specific substrates however, and in this perspective, the Yu group reported that homochiral norbornene derivatives were quite efficient, in combination with a pyridine ligand and, in some cases, a chiral BINOL-derived phosphate. The use of such catalytic systems could be successfully applied to the (hetero)arylation and alkylation of biarylmethylamines bearing a pyridinyl directing group [Scheme^^105<schr105>, Eq.^^(1)] and homobenzylamines bearing a nosyl group on the amine as directing group, through desymmetrization or kinetic resolution [Scheme^^105<xschr105>, Eq.^^(2)].[189a] Noteworthy, mechanistic studies and DFT calculations suggested that the desymmetrization process was occurring during the reversible formation of the aryl-norbornyl-palladium intermediate.[189b,c]

Other positions can also be functionalized, as demonstrated by the Maiti group which recently reported the *para*-selective arylation of a range of sulfonate, phosphonate, and aryl ethers. In this process, a complex scaffold is incorporated within the substrate to direct the palladium catalyst towards the *meta*-position prior to the norbornene insertion (Scheme^^106<schr106>).[190] Unfortunately, since both the *para*- and the *ortho*- positions could be functionalized after a first *meta*-C<C->H activation, only *ortho*,*ortho'*-disubstituted substrates were tolerated in this process to ensure *para* selectivity, which somehow restricts its synthetic usefulness despite its elegance.

As a reminder, the groups of Houk and Yu recently disclosed a template-assisted site-selective arylation of (iso)quinoline derivatives by elegantly combining both the non-covalent bonding strategy and the palladium/norbornene cooperative catalysis as discussed in section 6.3.[167e]

Last but not least, the Yu group further demonstrated that these "directed Catellani" processes were not limited to arylation and alkylation reactions by developing efficient *meta*-

selective amination, alkynylation and chlorination of Boc-protected anilines and phenols bearing a picolinyl directing group on the heteroatom (Scheme^^107<schr107>).[191]

Furthermore, the strategy could also be implemented to the C($sp^2$)<C->H functionalization of alkenes bearing a remote directing group. The group of Dong indeed reported in 2020 both the arylation and alkylation of substituted alkenes bearing an oxime directing group through the use of a more reactive peculiar imide-based norbornene. The functionalization occurred at the distal position following a proximal activation featuring excellent levels of both regio- and diastereo- selectivity (Scheme^^108<schr108>).[192]

While these modifications of the Catellani reaction using a norbornene transient mediator combined with a directing group proved to be rather efficient for a range of site-selective transformations of arenes and occasionally alkenes, some efforts have also been devoted to applying a similar strategy to indoles and pyrroles, as overviewed in the following section.

**7.2. Norbornene-mediated functionalization of indoles and pyrroles**

Modifications of the Catellani reaction have indeed been extensively implemented to the C2-selective functionalization of indoles and pyrroles over the last decade utilizing their deprotonation to provide an anchoring point for palladium.[193] Pioneered by the group of Bach in 2011 with the C2-selective direct alkylation of indoles with alkyl bromides, this process enabled the alkylation of a range of indoles with primary alkyl bromides in the presence of $Pd(MeCN)_2Cl_2$ along with norbornene as the transient directing mediator, in moderate to good yields [Scheme^^109<schr109>, Eq.^^(1)].[194a,b] Interestingly, this alkylation process could also be combined with a subsequent nucleophilic substitution at either positions 1 or 3, when using dibromoalkanes as coupling agents to give annelated indoles.[195] The Bach group further successfully extended this process to Boc-protected tryptophane methyl ester derivatives,[194c] and pyrroles [Scheme^^109<xschr109>,

Eq.^^(2)],[194d] prior to applying it to the syntheses of three different natural products, namely aspidospermidine, goniomitine and mycalazal.[194e] Inspired by these results, total syntheses of natural products and biologically relevant substances next successfully implemented this strategy as a key step.[196] Noteworthy, the process was also further extended to both the C2-selective trifluoroethylation of indoles provided that β-diketone ligands are used,[197] and to the synthesis of phosphonate-substituted indoles when using (iodomethyl)phosphonates as coupling partners.[198]

Supported by mechanistic investigations and since *N*-methyl-indole proved to be unreactive while C3-substituted substrates were properly alkylated, the mechanism of this transformation was suggested to proceed through the general catalytic cycle depicted in Scheme^^110<schr110>.[194b] The latter starts with a *N*-palladation of the indole or pyrrole from a Pd(II) catalyst prior to coordination of the norbornene transient mediator, whose insertion subsequently occurs to afford the corresponding palladium(II) species -- that could be isolated and characterized by XRD -- before the irreversible C2<C->H activation and further oxidative addition into the halide coupling partner, thus delivering the corresponding palladium(IV) species. Reductive elimination subsequently occurs to generate the corresponding C2-functionalized nitrogen-norbornyl-Pd(II) species. Norbornene extrusion through β-carbon elimination and further protodepalladation eventually affords the desired product and regenerates the Pd(II) catalyst.

In their first report, the Bach group could demonstrate that the reaction also proceeded smoothly with iodobenzene, thus paving the way for regioselective arylation transformations, as evidenced by the groups of Xue and Jiang in 2017 (Scheme^^111<schr111>).[199]

As a final note, while this process could only deliver C2-arylated indoles, a complementary C3-arylation method could be achieved using LiHMDS as both a base and a transient mediator, through carbopalladation of the C2<C->C3 bond of indoles, directed by

electrostatic interactions between the lithiated base and the palladium species (Scheme^^112<schr112>).[200]

## 8. Conclusions and Outlook

<?IMA tlsb=-2%?>With the growing demand for efficient, straightforward, cost-efficient, and sustainable processes to access increasingly complex molecules required in many essential fields such as medicinal chemistry, agrochemistry, polymer and material sciences, just to cite a few, metal-catalyzed processes are of growing importance. In this perspective, reactions based on C<C->H functionalization are especially attractive and have been extensively revisited over the last decades. In these reactions, and when the innate reactivity of the substrate cannot be used to control the regioselectivity or when it needs to be overridden, a directing group is typically used. While this usually results in efficient and selective processes, the strategy still suffers from limitations due to additional installation and cleavage steps inherent to the use of directing groups.

<?IMA tlsb=-2%?>An impressively efficient, elegant, and close to ideal solution to these issues has been found in the transient version of such directing groups that can be both introduced and removed in^^situ, often in a catalytic manner. As evidenced with all the examples overviewed in this review article, the use of these transient directing groups in synergy with transition-metal catalysis has proved to be remarkably powerful in terms of performance, atom economy as well as selectivity, thereby unlocking the development of highly appealing, attractive, and versatile transformations with broad substrate scopes, often with selectivities that cannot be attained otherwise relying on innate reactivity.

<?IMA tlsb=-2%?>Nevertheless, limitations still remain, and this field is not fully mature yet and in full development. Indeed, only a handful of functional groups have been utilized to transiently install a directing group into the substrate, and there is no doubt that the range of starting materials amenable to transiently directed reactions will exponentially grow

in the near future. Obviously, the dynamic requirement of installation and removal of the directing group in covalent systems limits the functional groups suitable but the non-covalent weak interactions offer huge possibilities there. A second limitation lies in the transition-metals, ligands and transient mediators utilized up to now. Indeed, noble metals such as rhodium, iridium and palladium have been most commonly utilized which is an important limitation to be addressed to extend these processes to other cheaper and more available base metals. The nature of the ligands and the transient directing mediators are equally important and a focus on readily available, simple ones featuring low molecular mass is important to ensure the attractiveness of the processes.

<?IMA tlsb=-2%?>Nonetheless, this thrilling field of catalysis has already proven its efficiency and it will undoubtedly continue to be developed further and implemented in both academic and industrial processes.

**Acknowledgements**

Our work was supported by the <cgs>Université libre de Bruxelles</cgs> (ULB), the <cgs>Federal Excellence of Science (EoS) program</cgs> (BIOFACT, Grant No. <cgn>O019618F</cgn>), the <cgs>Francqui Foundation</cgs>, and <cgs>FWO</cgs> (Research project and Scientific Research Network). All authors thank Dr. J. Annibaletto, Dr. J. Ling, Mr. S. Peruško and Mr. P. Thilmany (ULB) for careful proofreading of this manuscript and most sincerely thank the reviewers for the remarkable level of suggestions and corrections.

## Conflict of Interest

The authors declare no conflict of interest.

<lit1><lit_a><jnl>A. Suzuki, *Angew. Chem. Int. Ed.* **2011**, *50*, 6722--6737; *Angew. Chem.* **2011**, *123*, 6854--6869</jnl>; <lit_b><jnl>E.-I. Negishi, *Angew. Chem. Int. Ed.* **2011**, *50*, 6738--6764; *Angew. Chem.* **2011**, *123*, 6870--6897</jnl>; <lit_c><jnl>C.^^C.^^C. Johansson^^Seechurn, M.^^O. Kitching, T.^^J. Colacot, V. Snieckus, *Angew. Chem. Int. Ed.* **2012**, *51*, 5062--5085; *Angew. Chem.* **2012**, *124*, 5150--5174</jnl>.

<lit2>For selected books, see: <lit_a><book>*Palladium In Organic Synthesis* (Ed: J. Tsuji), Springer, Berlin, Heidelberg, **2005**</book>; <lit_b><book>*Palladium-Catalyzed Coupling Reactions: Practical Aspects and Future Developments* (Ed: Á. Moln, Wiley-VCH, Weinheim, **2013**</book>; <lit_c><book>C*opper-Mediated Cross-Coupling Reactions* (Eds: G. Evano, N. Blanchard), Wiley-VCH, Hoboken, **2013**</book>; <lit_d><book>*Rhodium Catalysis in Organic Synthesis: Methods and Reactions* (Ed: K. Tanaka), Wiley-VCH, Weinheim, **2019**</book>.

<lit3><book>B.^^U.^^W. Maes, C. Sambiagio in *Remote C-H Bond Functionalizations: Methods and Strategies in Organic Synthesis* (Eds: D. Maiti, S. Guin), Wiley-VCH, Weinheim, **2021**, pp. 343--382</book>.

<lit4>For recent review articles, see <lit_a><jnl>F. Zhang, D.^^R. Spring, *Chem. Soc. Rev.* **2014**, *43*, 6906--6919</jnl>; <lit_b><jnl>Z. Chen, B. Wang, J. Zhang, W. Yu, Z. Liu, Y. Zhang, *Org. Chem. Front.* **2015**, *2*, 1107--1295</jnl>; <lit_c><jnl>W.-H. Rao, B.-F. Shi, *Org. Chem. Front.* **2016**, *3*, 1028--1047</jnl>; <lit_d><jnl>C. Sambiagio, D. Schönbauer, R. Blieck, T. Dao-Huy, G. Pototschnig, P. Schaaf, T. Wiesinger, M. Farooq^^Zia, J. Wencel-Delord, T. Besset, B.^^U.^^W. Maes, M. Schnürch, *Chem. Soc. Rev.* **2018**, *47*, 6603--6743</jnl>; <lit_e><jnl>S. Rej, Y. Ano, N. Chatani, *Chem. Rev.* **2020**, *120*, 1788--1887</jnl>; <lit_f><jnl>K. Murali, L.^^A. Machado, R.^^L. Carvalho, L.^^F. Pedrosa, R. Mukherjee, E.^^N. da^^Silva, Júnior, D. Maiti*Chem. Eur. J.* **2021**, <url>https://doi.org/10.1002/chem.202101004</url></jnl>.

<lit5>For a selected recent review article, see: <jnl>J. Das, D. Kanti^^Mal, S. Maji, D. Maiti, *ACS Catal.* **2021**, *11*, 4205--4229</jnl>.

<lit6><lit_a><jnl>Y. Boutadla, D.^^L. Davies, S.^^A. Macgregor, A.^^I. Poblador-Bahamonde,*Dalton Trans.* **2009**, 5820--5831</jnl>; <lit_b><jnl>D. Lapointe, K. Fagnou, *Chem. Lett.* **2010**, *39*, 1118--1126</jnl>; <lit_c><jnl>L. Ackermann, *Chem.*

*Rev.* **2011**, *111*, 1315--1345</jnl>; <lit_d><jnl>D.^^L. Davies, S.^^A. Macgregor, C.^^L. McMullin, *Chem. Rev.* **2017**, *117*, 8649--8709</jnl>; <lit_e><jnl>B.^^P. Carrow, J. Sampson, L. Wang, *Isr. J. Chem.* **2020**, *60*, 230--258</jnl>; <lit_f><jnl>T. Rogge, J.^^C.^^A. Oliveira, R. Kuniyil, L. Hu, L. Ackermann, *ACS Catal.* **2020**, *10*, 10551--10558</jnl>.

<lit7><lit_a><jnl>H. Sun, N. Guimond, Y. Huang, *Org. Biomol. Chem.* **2016**, *14*, 8389--8397</jnl>; <lit_b><jnl>D.-S. Kim, W.-J. Park, C.-H. Jun, *Chem. Rev.* **2017**, *117*, 8977--9015</jnl>; <lit_c><jnl>Q. Zhao, T. Poisson, X. Pannecoucke, T. Besset, *Synthesis* **2017**, *49*, 4808--4826</jnl>; <lit_d><jnl>J. Lv, Q. Zhang, M. Cai, Y. Han, S. Luo, *Chem. Asian J.* **2018**, *13*, 740--753</jnl>; <lit_e><jnl>P. Gandeepan, L. Ackermann, *Chem.* **2018**, *4*, 199--222</jnl>; <lit_f><jnl>M. Ghosh, S. De^^Sarkar, *Asian J. Org. Chem.* **2018**, *7*, 1236--1255</jnl>; <lit_g><jnl>O.^^K. Rasheed, B. Sun, *ChemistrySelect* **2018**, *3*, 5689--5708</jnl>; <lit_h><jnl>T. Bhattacharya, S. Pimparkar, D. Maiti, *RSC Adv.* **2018**, *8*, 19456--19464</jnl>; <lit_i><jnl>S. St^^John-Campbell, J.^^A. Bull, *Org. Biomol. Chem.* **2018**, *16*, 4582--4595</jnl>; <lit_j><jnl>J.^^I. Higham, J.^^A. Bull, *Org. Biomol. Chem.* **2020**, *18*, 7291--7315</jnl>; <lit_k><jnl>B. Niu, K. Yang, B. Lawrence, H. Ge, *ChemSusChem* **2019**, *12*, 2955--2969</jnl>; <lit_l><jnl>D. Bag, P.^^K. Verma, S.^^D. Sawant, *Chem. Asian J.* **2020**, *16*, 3225--3238</jnl>; <lit_m><jnl>G. Liao, T. Zhang, Z.-K. Lin, B.-F. Shi, *Angew. Chem. Int. Ed.* **2020**, *59*, 19773--19786; *Angew. Chem.* **2020**, *132*, 19941--19954</jnl>; <lit_n><jnl>M.^^I. Lapuh, S. Mazeh, T. Besset, *ACS Catal.* **2020**, *10*, 12898--12919</jnl>; <lit_o><jnl>Y.-J. Wu, B.-F. Shi, *Chin. J. Org. Chem.* **2020**, *40*, 3517--3535</jnl>; <lit_p><jnl>B. Zu, Y. Guo, J. Ke, C. He, *Synthesis* **2021**, *53*, 2029--2042</jnl>; <lit_q><jnl>U. Dutta, S. Maiti, T. Bhattacharya, D. Maiti, *Science* **2021**, *372*, eabd5992</jnl>.

<lit8>For review articles on traceless directing groups, see: <lit_a><jnl>G. Rousseau, B. Breit, *Angew. Chem. Int. Ed.* **2011**, *50*, 2450--2494; *Angew. Chem.* **2011**, *123*, 2498--2543</jnl>; <lit_b><jnl>F. Zhang, D.^^R. Spring, *Chem. Soc. Rev.* **2014**, *43*, 6906--6919</jnl>; <lit_c><jnl>R. Rossi, M. Lessi, C. Manzini, G. Marianetti, F. Bellina, *Tetrahedron* **2016**, *72*, 1795--1837</jnl>; <lit_d><jnl>M. Font, J.^^M. Quibell, G.^^J.^^P. Perry, I. Larosa, *Chem. Commun.* **2017**, *53*, 5584--5597</jnl>; <lit_e><jnl>G. Rani, V. Luxami, K. Paul, *Chem. Commun.* **2020**, *56*, 12479--12521</jnl>.

<lit9>For an example, see: <jnl>H. Zeng, Z. Wang, C.-J. Li, *Angew. Chem. Int. Ed.* **2019**, *58*, 2859--2863; *Angew. Chem.* **2019**, *131*, 2885--2889</jnl>.

<lit10>For recent review articles on the Catellani reaction, see: <lit_a><jnl>M. Catellani, *Synlett* **2003**, *2003*, 298--313</jnl>; <lit_b><jnl>N. Della^^Ca', M. Fontana, E. Motti, M. Catellani, *Acc. Chem. Res.* **2016**, *49*, 1389--1400</jnl>; <lit_c><jnl>J. Wang, G. Dong, *Chem. Rev.* **2019**, *119*, 7478--7528</jnl>; <lit_d><jnl>H.-G. Cheng, S. Chen, R. Chen, Q. Zhou, *Angew. Chem. Int. Ed.* **2019**, *58*, 5832--5844; *Angew. Chem.* **2019**, *131*, 5890--5902</jnl>; <lit_e><jnl>R. Li, G. Dong, *J. Am. Chem. Soc.* **2020**, *142*, 17859--17875</jnl>.

<lit11>For recent review articles, see: <lit_a><jnl>S. Carboni, C. Gennari, L. Pignataro, U. Piarulli, *Dalton Trans.* **2011**, *40*, 4355--4373</jnl>; <lit_b><jnl>C.^^J. Brown, F.^^D. Toste, R.^^G. Bergman, K.^^N. Raymond, *Chem. Rev.* **2015**, *115*, 3012--3035</jnl>; <lit_c><jnl>A. Pappalardo, R. Puglisi, G. Trusso^^Sfrazzetto, *Catalysts* **2019**, *9*, 630--650</jnl>; <lit_d><jnl>C. Tan, D. Chu, X. Tang, Y. Liu, W. Xuan, Y. Cui, *Chem. Eur. J.* **2019**, *25*, 662--672</jnl>.

<lit12><jnl>Z. Huang, J.-P. Lumb, *ACS Catal.* **2019**, *9*, 521--555</jnl>.

<lit13><jnl>G.^^W. Parshall, W.^^H. Knoth, R.^^A. Schunn, *J. Am. Chem. Soc.* **1969**, *91*, 4990--4995</jnl>.

<lit14><jnl>L.^^N. Lewis, *Inorg. Chem.* **1985**, *24*, 4433--4435</jnl>.

<lit15><jnl>L.^^N. Lewis, J.^^F. Smith, *J. Am. Chem. Soc.* **1986**, *108*, 2728--2735</jnl>.

<lit16><jnl>S.^^A. Preston, D.^^C. Cupertino, P. Palma-Ramirez, D.^^J. Cole-Hamilton, *J. Chem. Soc. Chem. Commun.* **1986**, 977--978</jnl>.

<lit17><lit_a><jnl>R.^^B. Bedford, S.^^J. Coles, M.^^B. Hursthouse, M.^^E. Limmert, *Angew. Chem. Int. Ed*. **2003**, *42*, 112--114; *Angew. Chem.* **2003**, *115*, 116--118</jnl>; <lit_b><jnl>R.^^B. Bedford, M.^^E. Limmert, *J. Org. Chem.* **2003**, *68*, 8669--8682</jnl>.

<lit18><jnl>S. Oi, S.-I. Watanabe, S. Fukita, Y. Inoue, *Tetrahedron Lett.* **2003**, *44*, 8665--8668</jnl>.

<lit19><jnl>Q.-S. Liu, D.-Y. Wang, J.-F. Yang, Z.-Y. Ma, M. Ye, *Tetrahedron* **2017**, *73*, 3591--3595</jnl>.

<lit20><jnl>Y. Homma, K. Fukuda, N. Iwasawa, J. Takaya, *Chem. Commun.* **2020**, *56*, 10710--10713</jnl>.

<lit21><jnl>R.^^B. Bedford, M. Betham, A.^^J.^^M. Caffyn, J.^^P.^^H. Charmant, L.^^C. Lewis-Alleyne, P.^^D. Long, D. Polo-Cerón, S. Prashar, *Chem. Commun.* **2008**, 990--992</jnl>.

<lit22><jnl>R.^^B. Bedford, M.^^F. Haddow, R.^^L. Webster, C.^^J. Mitchell, *Org. Biomol. Chem.* **2009**, *7*, 3119--3127</jnl>.

<lit23><jnl>J.-F. Yang, R.-H. Wang, Y.-X. Wang, W.^^W. Yao, Q.-S. Liu, M. Ye, *Angew. Chem. Int. Ed.* **2016**, *55*, 14116--14120; *Angew. Chem.* **2016**, *128*, 14322--14326</jnl>.

<lit24><jnl>J.^^C. Lewis, J. Wu, R.^^G. Bergman, J.^^E. Ellman, *Organometallics* **2005**, *24*, 5737--5746</jnl>.

<lit25><jnl>M.^^C. Carrión, D.^^J. Cole-Hamilton, *Chem. Commun.* **2006**, 4527--4529</jnl>.

<lit26><lit_a><other>*Rhodium Catalyzed Hydroformylation* (Eds: P.^^W.^^N.^^M. Van^^Leeuwen, C. Claver), Springer, Dordrecht, **2002**</other>; <lit_b><jnl>R. Franke, D. Selent, A. Börner, *Chem. Rev.* **2012**, *112*, 5675--5732</jnl>; <lit_c><other>*Hydroformylation -- Fundamentals, Processes, and Applications in Organic Synthesis* (Eds: A. Börner, R. Franke), Wiley-VCH, Weinheim, **2016**</other>; <lit_d><book>B. Cornils, A. Börner, R. Franke, B. Zhang, E. Wiebus, K. Schmid in *Applied Homogeneous Catalysis with Organometallic Compounds: A Comprehensive Handbook in Four Volumes, Third Edition* (Eds: B. Cornils, W.^^A. Herrmann, M. Beller, R. Paciello), Wiley-VCH, Weinheim, **2018**, pp. 23--89</book>; <lit_e><jnl>S. Hanf, L.^^A. Rupflin, R. Gläser, S.^^A. Schunk, *Catalysts* **2020**, *10*, 510--545</jnl>.

<lit27><lit_a><jnl>C.^^U. Grünanger, B. Breit, *Angew. Chem. Int. Ed.* **2008**, *47*, 7346--7349; *Angew. Chem.* **2008**, *120*, 7456--7459</jnl>; <lit_b><jnl>C.^^U. Grünanger, B. Breit, *Angew. Chem. Int. Ed.* **2010**, *49*, 967--970; *Angew. Chem.* **2010**, *122*, 979--982</jnl>; <lit_c><jnl>Y. Ueki, H. Ito, I. Usui, B. Breit, *Chem. Eur. J.* **2011**, *17*, 8555--8558</jnl>; <lit_d><jnl>I. Usui, K. Nomura, B. Breit, *Org. Lett.* **2011**, *13*, 612--615</jnl>.

<lit28><lit_a><jnl>T.^^E. Lightburn, M.^^T. Dombrowski, K.^^L. Tan, *J. Am. Chem. Soc.* **2008**, *130*, 9210--9211</jnl>; <lit_b><jnl>C.^^L. Joe, T.^^P. Blaisdell, A.^^F. Geoghan, K.^^L. Tan, *J. Am. Chem. Soc.* **2014**, *136*, 8556--8559</jnl>; <lit_c><jnl>A.^^D. Worthy, M.^^M. Gagnon, M.^^T. Dombrowki, K.^^L. Tan, *Org. Lett.* **2009**, *11*, 2764--2767</jnl>; <lit_d><jnl>X. Sun, K. Frimpong, K.^^L. Tan, *J. Am.*

*Chem. Soc.* **2010**, *132*, 11841--11843</jnl>; <lit_e><jnl>T.^^E. Lightburn, O.^^A. De^^Paolis, K.^^H. Cheng, K.^^L. Tan, *Org. Lett.* **2011**, *13*, 2686--2689</jnl>; <lit_f><jnl>A.^^D. Worthy, C.^^L. Joe, T.^^E. Lightburn, K.^^L. Tan, *J. Am. Chem. Soc.* **2010**, *132*, 14757--14759</jnl>; <lit_g><jnl>C.^^L. Joe, K.^^L. Tan, *J. Org. Chem.* **2011**, *76*, 7590--7596</jnl>.

<lit29><lit_a><jnl>J.^^W. Suggs, *J. Am. Chem. Soc.* **1978**, *100*, 640--641</jnl>; <lit_b><jnl>J.^^W. Suggs, *J. Am. Chem. Soc.* **1978**, *101*, 489--489</jnl>.

<lit30><jnl>E.^^F. Landvatter, T.^^B. Rauchfuss, *Organomettallics* **1982**, *1*, 506--513</jnl>.

<lit31><lit_a><jnl>C.-H. Jun, H. Lee, J.-B. Hong, *J. Org. Chem.* **1997**, *62*, 1200--1201</jnl>; <lit_b><jnl>C.-H. Jun, D.-Y. Lee, J.-B. Hong, *Tetrahedron Lett.* **1997**, *38*, 6673--6676</jnl>; <lit_c><jnl>E.-A. Jo, C.-H. Jun, *Eur. J. Org. Chem.* **2006**, *2006*, 2504--2507</jnl>; <lit_d><jnl>N.^^R. Vautravers, D.^^D. Regent, B. Breit, *Chem. Commun.* **2011**, *47*, 6635--6637</jnl>.

<lit32><lit_a><jnl>C.-H. Jun, J.-H. Chung, D.-Y. Lee, A. Loupy, S. Chatti, *Tetrahedron Lett.* **2001**, *42*, 4803--4805</jnl>; <lit_b><jnl>A. Louy, S. Chatti, S. Delamare, D.-Y. Lee, J.-H. Chung, C.-H. Jun, *J. Chem. Soc. Perkin Trans. 1* **2002**, 1280--1285</jnl>.

<lit33><lit_a><jnl>R. Uson, L.^^A. Oro, R. Sariego, M.^^A. Esteruelas, *J. Organomet. Chem.* **1981**, *214*, 399--404</jnl>; <lit_b><jnl>R. Spogliarich, A. Tencich, J. Kaspar, M. Graziani, *J. Organomet. Chem.* **1982**, *240*, 453--459</jnl>.

<lit34><lit_a><jnl>C.-H. Jun, C.-W. Huh, S.-J. Na, *Angew. Chem. Int. Ed.* **1998**, *37*, 145--147; *Angew. Chem.* **1998**, *110*, 150--152</jnl>; <lit_b><jnl>E.-A. Jo, J.-H. Lee, C.-H. Jun, *Chem. Commun.* **2008**, 5779--5781</jnl>; <lit_c><jnl>C.-H. Jun, H.-S. Hong, C.-W. Huh, *Tetrahedron Lett.* **1999**, *40*, 8897--8900</jnl>; <lit_d><jnl>D.-W. Kim, S.-G.

Lim, C.-H. Jun, *Org. Lett.* **2006**, *8*, 2937--2940</jnl>; <lit_e><jnl>J.-W. Park, J.-H. Park, C.-H. Jun, *J. Org. Chem.* **2008**, *73*, 5598--5601</jnl>.

<lit35><lit_a><jnl>D.-Y. Lee, C.^^W. Moon, C.-H. Jun, *J. Org. Chem.* **2002**, *67*, 3945--3948</jnl>; <lit_b><jnl>C.-H. Lee, C.-H. Jun, *Synlett* **2018**, *29*, 736--741</jnl>.

<lit36><lit_a><jnl>C.-H. Jun, J.-B. Hong, *Org. Lett.* **1999**, *1*, 887--889</jnl>; <lit_b><jnl>C.-H. Jun, D.-Y. Lee, J.-B. Hong, *Angew. Chem. Int. Ed.* **2000**, *39*, 3070--3072; *Angew. Chem.* **2000**, *112*, 3214--3216</jnl>; <lit_c><jnl>C.-H. Jun, K.-Y. Chung, J.-B. Hong, *Org. Lett.* **2001**, *3*, 785--787</jnl>; <lit_d><jnl>C.-H. Jun, C.^^W. Moon, S.-G. Lim, H. Lee, *Org. Lett.* **2002**, *4*, 1595--1597</jnl>.

<lit37><jnl>E.^^V. Beletskiy, C. Sudheer, C.^^J. Douglas, *J. Org. Chem.* **2012**, *77*, 5884--5893</jnl>.

<lit38><lit_a><jnl>C.-H. Jun, D.-C. Hwang, *Polymer* **1998**, *39*, 7143--7147</jnl>; <lit_b><jnl>J.-H. Kim, C.-H. Jun, *Bull. Korean Chem. Soc*. **1999**, *20*, 27--29</jnl>; <lit_c><jnl>J.-H. Lee, E.-A. Jo, C.-H. Jun, *Synlett* **2009**, *2009*, 2647--2650</jnl>; <lit_d><jnl>J.-W. Park, C.-H. Jun, *J. Am. Chem. Soc.* **2010**, *132*, 7268--7269</jnl>; <lit_e><jnl>J.-W. Park, D.-S. Kim, M.-S. Kim, J.-H. Choi, J.-H. Jun, *Polym. Chem.* **2015**, *6*, 555--560</jnl>.

<lit39><lit_a><jnl>E.-A. Jo, C.-H. Jun, *Tetrahedron Lett.* **2009**, *50*, 3338--3340</jnl>; <lit_b><jnl>K.-M. Cha, H. Lee, J.-W. Park, Y. Lee, E.-A. Jo, C.-H. Jun, *Chem. Asian J.* **2011**, *6*, 1926--1930</jnl>; <lit_c><jnl>S.-G. Lim, C.-H. Jun, *Bull. Korean Chem. Soc.* **2004**, *25*, 1623--1624</jnl>; <lit_d><jnl>D.^^H. Lee, E.-A. Jo, J.-W. Park, C.-H. Jun, *Tetrahedron Lett.* **2010**, *51*, 160--163</jnl>; <lit_e><jnl>D.-Y. Lee, B.-S. Hong, E.-G. Cho, H. Lee, C.-H. Jun, *J. Am. Chem. Soc.* **2003**, *125*, 6372--6373</jnl>; <lit_f><jnl>K.-M. Cha, E.-A. Jo, C.-H. Jun, *Synlett* **2009**, *2009*, 2939--2942</jnl>.

<lit40><jnl>C.-H. Jun, H. Lee, J.-B. Hong, B.-I. Kwon, *Angew. Chem. Int. Ed.* **2002**, *41*, 2146--2147; *Angew. Chem.* **2002**, *114*, 2250--2251</jnl>.

<lit41><jnl>X.-H. Liu, H. Park, J.-H. Hu, Y. Hu, Q.-L. Zhang, B.-L. Wang, B. Sun, K.-S. Yeung, F.-L. Zhang, J.-Q. Yu, *J. Am. Chem. Soc.* **2017**, *139*, 888--896</jnl>.

<lit42><jnl>J. Xu, Y. Wang, Y. Li, X. Xu, Z. Jin, *Org. Lett.* **2017**, *19*, 1562--1565</jnl>.

<lit43><jnl>N. Thrimurtulu, A. Dey, A. Singh, K. Pal, D. Maiti, C.^^M.^^R. Volla, *Adv. Synth. Catal.* **2019**, *361*, 1441--1446</jnl>.

<lit44><jnl>J. Wang, C. Dong, L. Wu, M. Xu, J. Lin, K. Wei, *Adv. Synth. Catal.* **2018**, *360*, 3709--3715</jnl>.

<lit45><jnl>Y. Cheng, J. Zheng, C. Tian, Y. He, C. Zhang, Q. Tan, G. An, G. Li, *Asian J. Org. Chem.* **2019**, *8*, 526--531</jnl>.

<lit46><jnl>J. Xu, Y. Liu, J. Zhang, X. Xu, Z. Jin, *Chem. Commun.* **2018**, *54*, 689--692</jnl>.

<lit47><jnl>G. Liao, H.-M. Chen, Y.-N. Xia, B. Li, Q.-J. Yao, B.-F. Shi, *Angew. Chem. Int. Ed.* **2019**, *58*, 11464--11468; *Angew. Chem.* **2019**, *131*, 11586--11590</jnl>.

<lit48><jnl>B. Li, K. Seth, B. Niu, L. Pan, H. Yang, H. Ge, *Angew. Chem. Int. Ed.* **2018**, *57*, 3401--3405; *Angew. Chem.* **2018**, *130*, 3459--3463</jnl>.

<lit49><jnl>D. Mu, G. He, G. Chen, *Chem. Asian J.* **2018**, *13*, 2423--2426</jnl>.

<lit50><jnl>H. Lin, C. Wang, T. Bannister, T.^^M. Kamenecka, *Chem. Eur. J.* **2018**, *24*, 9535--9541</jnl>.

<lit51><lit_a><jnl>X.-Y. Chen, S. Ozturk, E.^^J. Sorensen, *Org. Lett.* **2017**, *19*, 1140--1143</jnl>; <lit_b><jnl>Y.-F. Wang, W.-G. Xu, B. Sun, Q.-Q. Yu, T.-J. Li, F.-L. Zhang, *J. Org. Chem.* **2019**, *84*, 13104--13111</jnl>.

<lit52><jnl>D.-Y. Wang, S.-H. Guo, G.-F. Pan, X.-Q. Zhu, Y.-R. Gao, Y.-Q. Wang, *Org. Lett.* **2018**, *20*, 1794--1797</jnl>.

<lit53><jnl>M.^^Y. Zhang, R.^^A. Barrow, *J. Org. Chem.* **2018**, *83*, 6776--6782</jnl>.

<lit54><jnl>S. Sun, J. Du, H. Fang, J. Lan, D. Wu, J. You, *Chem. Commun.* **2019**, *55*, 7518--7521</jnl>.

<lit55><book>R.^^M. Roberts, A.^^A. Khalaf, *Friedel-Crafts Alkylation Chemistry: a Century of Discovery*, Marcel Dekker, New York, **1984**</book>.

<lit56><lit_a><jnl>G. Evano, C. Theunissen, *Angew. Chem. Int. Ed.* **2019**, *58*, 7202--7236; *Angew. Chem.* **2019**, *131*, 7278--7314</jnl>; <lit_b><jnl>G. Evano, C. Theunissen, *Angew. Chem. Int. Ed.* **2019**, *58*, 7558--7598; *Angew. Chem.* **2019**, *131*, 7638--7680</jnl>.

<lit57><lit_a><jnl>C.-H. Jun, J.-B. Hong, Y.-H. Kim, K.-Y. Chung, *Angew. Chem. Int. Ed.* **2000**, *39*, 3440--3442; *Angew. Chem.* **2000**, *112*, 3582--3584</jnl>; <lit_b><jnl>C.-H. Jun, C.^^W. Moon, J.-B. Hong, S.-G. Lim, K.-Y. Chung, Y.-H. Kim, *Chem. Eur. J.* **2002**, *8*, 485--492</jnl>; <lit_c><jnl>G. Vo-Thanh, H. Lahrache, A. Loupy, I.-J. Kim, D.-H. Chang, C.-H. Jun, *Tetrahedron* **2004**, *60*, 5539--5543</jnl>.

<lit58><jnl>Y. Kuninobu, Y. Nishina, M. Shouho, K. Takai, *Angew. Chem. Int. Ed.* **2006**, *45*, 2766--2768; *Angew. Chem.* **2006**, *118*, 2832--2834</jnl>.

<lit59><lit_a><jnl>Z. Guan, S. Chen, Y. Huang, H. Yao, *Org. Lett.* **2019**, *21*, 3959--3962</jnl>; <lit_b><jnl>Z.-Y. Li, H.^^H.^^C. Lakmal, X. Qian, Z. Zhu, B. Donnadieu, S.^^J. McClain, X. Xu, X. Cui, *J. Am. Chem. Soc.* **2019**, *141*, 15730--15736</jnl>; <lit_c><jnl>G. Li, Q. Liu, L. Vasametty, W. Guo, J. Wang, *Angew. Chem. Int. Ed.* **2020**, *59*, 3475--3479; *Angew. Chem.* **2020**, *132*, 3503--3507</jnl>.

<lit60><jnl>F. Li, Y. Zhou, H. Yang, D. Liu, B. Sun, F.-L. Zhang, *Org. Lett.* **2018**, *20*, 146--149</jnl>.

<lit61><jnl>X.-Y. Chen, E.^^J. Sorensen, *Chem. Sci.* **2018**, *9*, 8951--8956</jnl>.

<lit62><jnl>X.-Y. Chen, E.^^J. Sorensen, *J. Am. Chem. Soc*. **2018**, *140*, 2789--2792</jnl>.

<lit63><lit_a><jnl>G. Liao, B. Li, H.-M. Chen, Q.-J. Yao, Y.-N. Xia, J. Luo, B.-F. Shi, *Angew. Chem. Int. Ed.* **2018**, *57*, 17151--17155; *Angew. Chem.* **2018**, *130*, 17397--17401</jnl>; <lit_b><jnl>H.-M. Chen, S. Zhang, G. Liao, Q.-J. Yao, X.-T. Xu, K. Zhang, B.-F. Shi, *Organometallics* **2019**, *38*, 4022--4028</jnl>.

<lit64><lit_a><jnl>P.^^W. Tan, N.^^A.^^B. Juwaini, J. Seayad, *Org. Lett.* **2013**, *15*, 5166--5169</jnl>; <lit_b><jnl>G. Li, J. Jijun, H. Xie, J. Wang, *Chem. Eur. J.* **2019**, *25*, 4688--4694</jnl>.

<lit65><jnl>H.-M. Chen, G. Liao, C.-K. Xu, Q.-J. Yao, S. Zhang, B.-F. Shi, *CCS Chem.* **2021**, *3*, 455--465</jnl>.

<lit66><jnl>X. Liu, Z. Wang, Q. Chen, M.-Y. He, L. Wang, *Appl. Organomet. Chem.* **2018**, *32*, e4039</jnl>.

<lit67><jnl>Richa, R. Kumar, X. Zhang, W. Su, *Org. Chem. Front.* **2020**, *7*, 2965--2974</jnl>.

<lit68><lit_a><jnl>K.^^M. Engle, J.-Q. Yu, *J. Org. Chem.* **2013**, *78*, 8927--8955</jnl>; <lit_b><jnl>Q. Shao, K. Wu, Z. Zhuang, S. Qian, J.-Q. Yu, *Acc. Chem. Res.* **2020**, *53*, 833--851</jnl>.

<lit69><jnl>S. Bag, S. Jana, S. Pradhan, S. Bhowmick, N. Goswami, S.^^K. Sinha, D. Maiti, *Nat. Commun.* **2021**, *12*, 1393</jnl>.

<lit70><jnl>Q.-J. Yao, S. Zhang, B.-B. Zhan, B.-F. Shi, *Angew. Chem. Int. Ed.* **2017**, *56*, 6617--6621; *Angew. Chem.* **2017**, *129*, 6717--6721</jnl>.

<lit71><jnl>H. Song, Y. Li, Q.-J. Yao, L. Jin, L. Liu, Y.-H. Liu, B.-F. Shi, *Angew. Chem. Int. Ed.* **2020**, *59*, 6576--6580; *Angew. Chem.* **2020**, *132*, 6638--6642</jnl>.

<lit72><jnl>J. Zhang, Q. Xu, J. Wu, J. Fan, M. Xie, *Org. Lett.* **2019**, *21*, 6361--6365</jnl>.

<lit73><jnl>J. Fan, Q.-J. Yao, Y.-H. Liu, G. Liao, S. Zhang, B.-F. Shi, *Org. Lett.* **2019**, *21*, 3352--3356</jnl>.

<lit74><jnl>U. Dhawa, C. Tian, T. Wdowik, J.^^C.^^A. Oliveira, J. Hao, L. Ackermann, *Angew. Chem. Int. Ed.* **2020**, *59*, 13451--13457; *Angew. Chem.* **2020**, *132*, 13553--13559</jnl>.

<lit75><jnl>S. Chen, J. Yu, Y. Jiang, F. Chen, J. Cheng, *Org. Lett.* **2013**, *15*, 4754--4757</jnl>.

<lit76><jnl>Y. Kuninobu, T. Matsuki, K. Takai, *Org. Lett.* **2010**, *12*, 2948--2950</jnl>.

<lit77><jnl>P. Zhao, F. Wang, K. Han, X. Li, *Org. Lett.* **2012**, *14*, 5506--5509</jnl>.

<lit78><jnl>Y. Shang, K. Jonnada, S.^^L. Yedage, H. Tu, X. Zhang, X. Lou, S. Huang, W. Su, *Chem. Commun.* **2019**, *55*, 9547--9550</jnl>.

<lit79><lit_a><jnl>G. Liao, Q.-J. Yao, Z.-Z. Zhang, Y.-J. Wu, D.-Y. Huang, B.-F. Shi, *Angew. Chem. Int. Ed.* **2018**, *57*, 3661--3665; *Angew. Chem.* **2018**, *130*, 3723--3727</jnl>; <lit_b><jnl>S. Zhang, Q.-J. Yao, G. Liao, X. Li, H. Li, H.-M. Chen, X. Hong, B.-F. Shi, *ACS Catal.* **2019**, *9*, 1956--1961</jnl>.

<lit80><jnl>E. Tan, L.^^J. Nannini, O. Stoica, A.^^M. Echavarren, *Org. Lett.* **2021**, *23*, 1263--1268</jnl>.

<lit81><lit_a><jnl>D.^^S. Surry, S.^^L. Buchwald, *Angew. Chem. Int. Ed.* **2008**, *47*, 6338--6361; *Angew. Chem.* **2008**, *120*, 6438--6461</jnl>; <lit_b><jnl>J. Hartwig, *Acc. Chem. Res.* **2008**, *41*, 1534--1544</jnl>; <lit_c><other>*Amination and Formation of sp2^^C-N Bonds* (Eds: M. Taillefer, D. Ma), Springer-Verlag, Berlin, Heidelberg, **2013**</other>; <lit_d><jnl>J. Bariwal, E. Van^^der^^Eycken, *Chem. Soc. Rev.* **2013**, *42*, 9283--9303</jnl>; <lit_e><jnl>P. Ruiz-Castillo, S.^^L. Buchwald, *Chem. Rev.* **2016**, *116*, 12564--12649</jnl>.

<lit82><lit_a><jnl>Y.-F. Zhang, B. Wu, Z.-J. Shi, *Chem. Eur. J.* **2016**, *22*, 17808--17812</jnl>; <lit_b><jnl>D. Mu, X. Wang, G. Chen, G. He, *J. Org. Chem.* **2017**, *82*, 4497--4503</jnl>; <lit_c><jnl>O.^^K. Rasheed, *Synlett* **2018**, *29*, 1033--1036</jnl>.

<lit83><lit_a><jnl>X. Wang, S. Song, N. Jiao, *Chin. J. Chem.* **2018**, *36*, 213--216</jnl>; <lit_b><jnl>C.-F. Liu, M. Liu, J.-S. Sun, C. Li, L. Dong, *Org. Chem. Front.* **2018**, *5*, 2115--2119</jnl>; <lit_c><jnl>A.^^E. Hande, V.^^B. Ramesh, K.^^R. Prabhu, *Chem. Commun.* **2018**, *54*, 12113--12116</jnl>; <lit_d><jnl>J. Huang, J. Ding, T.-M. Ding, S. Zhang, Y. Wang, F. Sha, S.-Y. Zhang, X.-Y. Wu, Q. Li, *Org. Lett.* **2019**, *21*, 7342--7345</jnl>; <lit_e><jnl>B. Khan, V. Dwivedi, B. Sundararaju, *Adv. Synth. Catal.* **2020**, *362*, 1195--1200</jnl>.

<lit84><jnl>K. Yoo, J. Lee, M.^^H. Park, Y. Kim, H.^^J. Kim, M. Kim, *J. Org. Chem.* **2020**, *85*, 6233--6241</jnl>.

<lit85><jnl>Y. Wu, N. Liu, M. Qi, H. Qiao, X. Lu, L. Ma, Y. Zhou, F.-L. Zhang, *Org. Lett.* **2021**, *23*, 3923--3927</jnl>.

<lit86><lit_a><jnl>W. Hu, Q. Zheng, S. Sun, J. Cheng, *Chem. Commun.* **2017**, *53*, 6263--6266</jnl>; <lit_b><jnl>J. Shen, X. Liu, L. Wang, Q. Chen, M. He, *Synth. Commun.* **2018**, *48*, 1354--1362</jnl>; <lit_c><jnl>S. Kim, S.^^H. Han, N.^^K. Mishra, R. Chun,

Y.^^H. Jung, H.^^S. Kim, J.^^S. Park, I.^^S. Kim, *Org. Lett.* **2018**, *20*, 4010--4014</jnl>.

<lit87><lit_a><jnl>F. Li, Y. Zhou, H. Yang, Z. Wang, Q. Yu, F.-L. Zhang, *Org. Lett.* **2019**, *21*, 3692--3695</jnl>; <lit_b><jnl>Q. Yong, B. Sun, F.-L. Zhang, *Tetrahedron Lett.* **2019**, *60*, 151263--151266</jnl>.

<lit88><jnl>Q. Wu, Y.-J. Mao, K. Zhou, S. Wang, L. Chen, Z.-Y. Xu, S.-J. Lou, D.-Q. Xu, *Chem. Commun.* **2021**, *57*, 4544--4547</jnl>.

<lit89><jnl>X.-Y. Chen, S. Ozturk, E.^^J. Sorensen, *Org. Lett.* **2017**, *19*, 6280--6283</jnl>.

<lit90><jnl>J. Jiang, D. Yuan, C. Ma, W. Song, Y. Lin, L. Hu, Y. Zhang, *Org. Lett.* **2021**, *23*, 279--284</jnl>.

<lit91><jnl>L. Jin, X.-L. Zhang, R.-L. Guo, M.-Y. Wang, Y.-R. Gao, Y.-Q. Wang, *Org. Lett.* **2021**, *23,* 1921--1927</jnl>.

<lit92><jnl>R. Bisht, B. Chattopadhyay, *J. Am. Chem. Soc.* **2016**, *138*, 84--87</jnl>.

<lit93><jnl>S. Rej, N. Chatani, *J. Am. Chem. Soc.* **2021**, *143*, 2920--2929</jnl>.

<lit94><jnl>H. Qiao, B. Sun, Q. Yu, Y.-Y. Huang, Y. Zhou, F.-L. Zhang, *Org. Lett.* **2019**, *21*, 6914--6918</jnl>.

<lit95><jnl>Y.-J. Wu, Q.-J. Yao, H.-M. Chen, G. Liao, B.-F. Shi, *Sci. China Chem.* **2020**, *63*, 875--880</jnl>.

<lit96><lit_a><jnl>S. Kopf, H. Neumann, M. Beller, *Chem. Commun.* **2021**, *57*, 1137--1140</jnl>; <lit_b><jnl>S. Kopf, F. Ye, H. Neumann, M. Beller, *Chem. Eur. J.* **2021**, *27*, 9768--9773</jnl>.

<lit97><jnl>C.-H. Jun, C.^^W. Moon, Y.-M. Kim, H. Lee, J.^^H. Lee, *Tetrahedron Lett.* **2002**, *43*, 4233--4236</jnl>.

<lit98><jnl>F.-L. Zhang, K. Hong, T.-J. Li, H. Park, J.-Q. Yu, *Science* **2016**, *351*, 252--256</jnl>.

<lit99><jnl>F. Ma, M. Lei, L. Hu, *Org. Lett.* **2016**, *18*, 2708--2711</jnl>.

<lit100><jnl>H. Park, K. Yoo, B. Jung, M. Kim, *Tetrahedron* **2018**, *74*, 2048--2055</jnl>.

<lit101><jnl>F. Wen, Z. Li, *Adv. Synth. Catal.* **2020**, *362*, 133--138</jnl>.

<lit102><jnl>L. Lei, P. Wu, Z. Liu, J. Lou, *Tetrahedron Lett.* **2021**, *67*, 152865--152868</jnl>.

<lit103><jnl>J. Chen, C. Bai, H. Ma, D. Liu, Y.-S. Bao, *Chin. Chem. Lett.* **2021**, *32*, 465--469</jnl>.

<lit104><jnl>C. Reddy, J.^^Y. Shaikh, R.^^G. Bhat, *J. Org. Chem.* **2020**, *85*, 6924--6934</jnl>.

<lit105><jnl>F. Wen, Z. Li, *Synth. Commun.* **2020**, *50*, 3462--3474</jnl>.

<lit106><jnl>M. Ding, W. Hua, M. Liu, F. Zhang, *Org. Lett.* **2020**, *22*, 7419--7423</jnl>.

<lit107><lit_a><jnl>M. Tang, Q. Yu, Z. Wang, C. Zhang, B. Sun, Y. Yi, F.-L. Zhang, *Org. Lett.* **2018**, *20*, 7620--7623</jnl>; <lit_b><jnl>Z. Wang, W. Dong, B. Sun, Q. Yu, F.-L. Zhang, *Tetrahedron* **2019**, *75*, 4031--4041</jnl>; <lit_c><jnl>W. Dong, Z. Hu, Z. Wang, B. Sun, X. Zhang, F.-L. Zhang, *Tetrahedron Lett.* **2019**, *60*, 151299--151302</jnl>.

<lit108><jnl>L. Jin, J. Wang, G. Dong, *Angew. Chem. Int. Ed.* **2018**, *57*, 12352--12355; *Angew. Chem.* **2018**, *130*, 12532--12535</jnl>.

<lit109><jnl>K. Yang, Q. Li, Y. Liu, G. Li, H. Ge, *J. Am. Chem. Soc.* **2016**, *138*, 12775--12778</jnl>.

<lit110><jnl>S. St^^John-Campbell, A.^^J.^^P. White, J.^^A. Bull, *Chem. Sci.* **2017**, *8*, 4840--4847</jnl>.

<lit111><jnl>S. St^^John-Campbell, J.^^A. Bull, *Chem. Commun.* **2019**, *55*, 9172--9175</jnl>.

<lit112><jnl>B.-B. Gou, H.-F. Liu, J. Chen, L. Zhou, *Org. Lett.* **2019**, *21*, 7084--7088</jnl>.

<lit113><jnl>S. St^^John-Campbell, A.^^J.^^P. White, J.^^A. Bull, *Org. Lett.* **2020**, *22*, 1807--1812</jnl>.

<lit114><jnl>C. Dong, L. Wu, J. Yao, K. Wei, *Org. Lett.* **2019**, *21*, 2085--2089</jnl>.

<lit115><jnl>B. Li, B. Lawrence, G. Li, H. Ge, *Angew. Chem. Int. Ed.* **2020**, *59*, 3078--3082; *Angew. Chem.* **2020**, *132*, 3102--3106</jnl>.

<lit116><jnl>K. Hong, H. Park, J.-Q. Yu, *ACS Catal.* **2017**, *7*, 6938--6941</jnl>.

<lit117><jnl>L. Pan, K. Yang, G. Li, H. Ge, *Chem. Commun.* **2018**, *54*, 2759--2762</jnl>.

<lit118><jnl>Y.Wang, G. Wu, X. Xu, B. Pang, S. Liao, Y. Ji, *J. Org. Chem.* **2021**, *86*, 7296--7303</jnl>.

<lit119><jnl>L.-J. Xiao, K. Hong, F. Luo, L. Hu, W.^^R. Ewing, K.-S. Yeung, J.-Q. Yu, *Angew. Chem. Int. Ed.* **2020**, *59*, 9594--9600; *Angew. Chem.* **2020**, *132*, 9681--9687</jnl>.

<lit120><jnl>P.^^A. Provencher, K.^^L. Bay, J.^^F. Hoskin, K.^^N. Houk, J.-Q. Yu, E.^^J. Sorensen, *ACS Catal.* **2021**, *11*, 3115--3127</jnl>.

<lit121><jnl>X.-L. Zhang, G.-F. Pan, X.-Q. Zhu, R.-L. Guo, Y.-R. Gao, Y.-Q. Wang, *Org. Lett.* **2019**, *21*, 2731--2735</jnl>.

<lit122><lit_a><jnl>Z. Wang, B.^^J. Reinus, G. Dong, *J. Am. Chem. Soc.* **2012**, *134*, 13954--13957</jnl>; <lit_b><jnl>F. Mo, G. Dong, *Science* **2014**, *345*, 68--72</jnl>;

<lit_c><jnl>D. Xing, X. Qi, D. Marchant, P. Liu, G. Dong, *Angew. Chem. Int. Ed.* **2019**, *58*, 4366--4370; *Angew. Chem.* **2019**, *131*, 4410--4414</jnl>; <lit_d><jnl>H.^^N. Lim, G. Dong, *Angew. Chem. Int. Ed.* **2015**, *54*, 15294--15298; *Angew. Chem.* **2015**, *127*, 15509--15513</jnl>; <lit_e><jnl>F. Mo, H.^^N. Lim, G. Dong, *J. Am. Chem. Soc.* **2015**, *137*, 15518--15527</jnl>; <lit_f><jnl>Y. Xu, M.^^C. Young, G. Dong, *J. Am. Chem. Soc.* **2017**, *139*, 5716--5719</jnl>.

<lit123><jnl>H. Park, P. Verma, K. Hong, J.-Q. Yu, *Nat. Chem.* **2018**, *10*, 755--762</jnl>.

<lit124><jnl>J. Chen, C. Bai, X. Tong, D. Liu, Y.-S. Bao, *RSC Adv.* **2020**, *10*, 12192--12196</jnl>.

<lit125><lit_a><jnl>B. Schönecker, T. Zheldakova, Y. Liu, M. Kötteritzsch, W. Günther, H. Görls, *Angew. Chem. Int. Ed.* **2003**, *42*, 3240--3244; *Angew. Chem.* **2003**, *115*, 3361--3365</jnl>; <lit_b><jnl>B. Schönecker, T. Zheldakova, C. Lange, W. Günther, H. Görls, M. Bohl, *Chem. Eur. J.* **2004**, *3*, 6029--6042</jnl>.

<lit126><jnl>Y.^^Y. See, A.^^T. Herrmann, Y. Aihara, P.^^S. Baran, *J. Am. Chem. Soc.* **2015**, *137*, 13776--13779</jnl>.

<lit127><jnl>T. Mu, B. Wei, D. Zhu, B. Yu, *Nat. Commun.* **2020**, *11*, 4371</jnl>.

<lit128><lit_a><book>L.^^L. Schafer, J.^^C.-H. Yim, N. Yonson in *Metal-Catalyzed Cross-Coupling Reactions and More, 1, 2 and 3* (Eds: A. de Meijere, S. Bräse, M. Oestreich, Wiley-VCH, Weinheim, **2014**, pp. 1135--1258</book>; <lit_b><jnl>J.^^A. Gurak, Jr., K.^^M. Engle, *Synlett* **2017**, *28*, 2057--2065</jnl>; <lit_c><jnl>C. Lepori, J. Hannedouche, *Synthesis* **2017**, *49*, 1158--1167</jnl>; <lit_d><jnl>J. Hannedouche, E. Schulz, *Organometallics* **2018**, *37*, 4313--4326</jnl>; <lit_e><jnl>J.^^M. Ganley, P.^^R.^^D. Murray, R.^^R. Knowles, *ACS Catal.* **2020**, *10*, 11712--11738</jnl>.

<lit129><jnl>C. He, W.^^G. Whitehurst, M.^^J. Gaunt, *Chem.* **2019**, *5*, 1031--1058</jnl>.

<lit130><jnl>Y. Xu, M.^^C. Young, C. Wang, D.^^M. Magness, G. Dong, *Angew. Chem. Int. Ed.* **2016**, *55*, 9084--9087; *Angew. Chem.* **2016**, *128*, 9230--9233</jnl>.

<lit131><lit_a><jnl>Y. Wu, Y.-Q. Chen, T. Liu, M.^^D. Eastgate, J.-Q. Yu, *J. Am. Chem. Soc.* **2016**, *138*, 14554--14557</jnl>; <lit_b><other>J.-Q. Yu (The Scripps Research Institute), WO 080897, **2018**</other>.

<lit132><jnl>H. Ha, H.^^J. Choi, H. Park, Y. Gwon, J. Lee, J. Kwak, M. Kim, B. Jung, *Eur. J. Org. Chem.* **2021**, *2021*, 1136--1145</jnl>.

<lit133><jnl>A. Yada, W. Liao, Y. Sato, M. Murakami, *Angew. Chem. Int. Ed.* **2017**, *56*, 1073--1076; *Angew. Chem.* **2017**, *129*, 1093--1096</jnl>.

<lit134><jnl>Y. Liu, H. Ge, *Nat. Chem.* **2017**, *9*, 26--32</jnl>.

<lit135><jnl>Z. Wang, Y. Fu, Q. Zhang, H. Liu, J. Wang, *J. Org. Chem.* **2020**, *85*, 7683--7693</jnl>.

<lit136><jnl>S. St^^John-Campbell, A.^^K. Ou, J.^^A. Bull, *Chem. Eur. J.* **2018**, *24*, 17838--17843</jnl>.

<lit137><jnl>X.-X. Hu, J.-B. Liu, L.-L. Wang, F. Huang, C.-Z. Sun, D.-Z. Chen, *Org. Chem. Front.* **2018**, *5*, 1670--1678</jnl>.

<lit138><jnl>Y.-Q. Chen, Z. Wang, Y. Wu, S.^^R. Wisniewski, J.^^X. Qiao, W.^^R. Ewing, M.^^D. Eastgate, J.-Q. Yu, *J. Am. Chem. Soc.* **2018**, *140*, 17884--17894</jnl>.

<lit139><jnl>Y.-Q. Chen, S. Singh, Y. Wu, Z. Wang, W. Hao, P. Verma, J.^^X. Qiao, R.^^B. Sunoj, J.-Q. Yu, *J. Am. Chem. Soc.* **2020**, *142*, 9966--9974</jnl>.

<lit140><jnl>B. Su, A. Bunescu, Y. Qiu, S.^^J. Zuend, M. Ernst, J.^^F. Hartwig, *J. Am. Chem. Soc.* **2020**, *142*, 7912--7919</jnl>.

<lit141><jnl>Y.-Q. Chen, Y. Wu, Z. Wang, J.^^X. Qiao, J.-Q. Yu, *ACS Catal.* **2020**, *10*, 5657--5662</jnl>.

<lit142><lit_a><jnl>C.-H. Jun, H. Lee, *J. Am. Chem. Soc.* **1999**, *121*, 880--881</jnl>; <lit_b><jnl>J.-A. Ahn, D.-H. Chang, Y.^^J. Park, Y.^^R. Yon, A. Loupy, C.-H. Jun, *Adv. Synth. Catal.* **2006**, *348*, 55--58</jnl>; <lit_c><jnl>C.-H. Jun, D.-Y. Lee, Y.-H. Kim, H. Lee, *Organometallics* **2001**, *20*, 2928--2931</jnl>.

<lit143><lit_a><jnl>H.^^M. Ko, G. Dong, *Nat. Chem.* **2014**, *6*, 739--744</jnl>; <lit_b><jnl>Z.-Q. Rong, H.^^N. Lim, G. Dong, *Angew. Chem. Int. Ed.* **2018**, *57*, 475--479; *Angew. Chem.* **2018**, *130*, 484--488</jnl>; <lit_c><jnl>Y. Xia, S. Ochi, G. Dong, *J. Am. Chem. Soc.* **2019**, *141*, 13038--13042</jnl>.

<lit144><jnl>Y. Xue, G. Dong, *J. Am. Chem. Soc.* **2021**, *143*, 8272--8277</jnl>.

<lit145><lit_a><jnl>Y. Xia, G. Lu, P. Liu, G. Dong, *Nature* **2016**, *539*, 546--550</jnl>; <lit_b><jnl>Y. Xia, J. Wang, G. Dong, *Angew. Chem. Int. Ed.* **2017**, *56*, 2376--2380; *Angew. Chem.* **2017**, *129*, 2416--2420</jnl>; <lit_c><jnl>Y. Xia, J. Wang, G. Dong, *J. Am. Chem. Soc.* **2018**, *140*, 5347--5351</jnl>.

<lit146><jnl>G.-W. Wang, O.^^O. Sokolova, T.^^A. Young, E.^^M.^^S. Christodoulou, C.^^P. Butts, J.^^F. Bower, *J. Am. Chem. Soc.* **2020**, *142*, 19006--19011</jnl>.

<lit147><lit_a><jnl>X. Zhang, H. Zheng, J. Li, F. Xu, J. Zhao, H. Yan, *J. Am. Chem. Soc.* **2017**, *139*, 14511--14517</jnl>; <lit_b><jnl>X. Zhang, H. Yan, *Chem. Sci.* **2018**, *9*, 3964--3969</jnl>.

<lit148><lit_a><jnl>L.^^J. Oxoby, Z.-Q. Li, V.^^T. Tran, T.^^G. Erbay, R. Deng, P. Liu, K.^^M. Engle, *Angew. Chem. Int. Ed.* **2020**, *59*, 8885--8890; *Angew. Chem.* **2020**, *132*, 8970--8975</jnl>; <lit_b><jnl>Z. Liu, L.^^J. Oxtoby, M. Liu, Z.-Q. Li, V.^^T. Tran, Y. Gao, K.^^M. Engle, *J. Am. Chem. Soc.* **2021**, *143*, 8962--8969</jnl>.

<lit149><lit_a><jnl>M. Kapoor, D. Liu, M.^^C. Young, *J. Am. Chem. Soc.* **2018**, *140*, 6818--6822</jnl>; <lit_b><jnl>M. Kapoor, P. Chand-Thakuri, M.^^C. Young, *J. Am. Chem. Soc.* **2019***, 141*, 7980--7989</jnl>.

<lit150><lit_a><jnl>J. Luo, S. Preciado, I. Larrosa, *J. Am. Chem. Soc.* **2014**, *136*, 4109--4112</jnl>; <lit_b><jnl>M. Font, A.^^R.^^A. Spencer, I. Larrosa, *Chem. Sci.* **2018**, *9*, 7133--7137</jnl>; <lit_c><jnl>A.^^R.^^A. Spencer, R. Korde, M. Font, I. Larrosa, *Chem. Sci.* **2020**, *11*, 4204--4208</jnl>.

<lit151><lit_a><jnl>J. Meeuwissen, J.^^N.^^H. Reek, *Nat. Chem.* **2010**, *2*, 615--621</jnl>; <lit_b><jnl>H.^^J. Davis, R.^^J. Phipps, *Chem. Sci.* **2017**, *8*, 864--877</jnl>; <lit_c><jnl>C. Haldar, M.^^E. Hoque, R. Bisht, B. Chattopadhyay, *Tatrahedron Lett.* **2018**, *59*, 1269--1277</jnl>; <lit_d><jnl>N.^^R. Mote, S.^^H. Chikkali, *Chem. Asian J.* **2018**, *13*, 3623--3646; G. Meng, N.^^Y.^^S. Lam, E.^^R. Lucas, T.^^G. Saint-Denis, P. Verma, N. Cheksin, J.-Q. Yu, *J. Am. Chem. Soc.* **2020**, *142*, 10571--10591</jnl>; <lit_e><jnl>R.^^S.^^J. Proctor, A.^^C. Colgan, R.^^J. Phipps, *Nat. Chem.* **2020**, *12*, 990--1004</jnl>; <lit_f><jnl>G. Liao, Y.-J. Wu, B.-F. Shi, *Acta Chim. Sin.* **2020**, *78*, 289--298</jnl>.

<lit152>For representative examples, see: <lit_a><jnl>P.-A.^^R. Breuil, F.^^W. Patureau, J.^^N.^^H. Reek, *Angew. Chem. Int. Ed.* **2009**, *48*, 2162--2165; *Angew. Chem.* **2009**, *121*, 2196--2199</jnl>; <lit_b><jnl>P. Dydio, C. Rubay, T. Gadzikwa, M. Lutz, J.^^N.^^H. Reek, *J. Am. Chem. Soc.* **2011**, *133*, 17176--17179</jnl>; <lit_c><jnl>Q. Zhao, J. Wen, R. Tan, K. Huang, P. Metola, R. Wang, E.^^V. Anslyn, X. Zhang, *Angew. Chem. Int. Ed.* **2014**, *53*, 8467--8470; *Angew. Chem.* **2014**, *126*, 8607--8610</jnl>.

<lit153><lit_a><jnl>T. Šmejkal, B. Breit, *Angew. Chem. Int. Ed.* **2007**, *47*, 311--315; *Angew. Chem.* **2007**, *120*, 317--321</jnl>; <lit_b><jnl>T. Šmejkal, D. Gribkov, J. Geier, M.

Keller, B. Breit, *Chem. Eur. J.* **2010**, *16*, 2470--2478</jnl>; <lit_c><jnl>T. Šmejkal, B. Breit, *Angew. Chem. Int. Ed.* **2008**, *47*, 3946--3949; *Angew. Chem.* **2008**, *120*, 4010--4013</jnl>; <lit_d><jnl>L. Diab, U. Gellrich, B. Breit, *Chem. Commun.* **2013**, *49*, 9737--9739</jnl>; <lit_e><jnl>W. Fang, B. Breit, *Angew. Chem. Int. Ed.* **2018**, *57*, 14817--14821; *Angew. Chem.* **2018**, *130*, 15033--15037</jnl>; <lit_f><jnl>W. Fang, F. Bauer, Y. Dong, B. Breit, *Nat. Commun.* **2019**, *10*, 4868</jnl>; <lit_g><jnl>L. Diab, T. Šmejkal, J. Geier, B. Breit, *Angew. Chem. Int. Ed.* **2009**, *48*, 8022--8026; *Angew. Chem.* **2009**, *121*, 8166--8170</jnl>; <lit_h><jnl>D. Fuchs, G. Rousseau, L. Diab, U. Gellrich, B. Breit, *Angew. Chem. Int. Ed.* **2012**, *51*, 2178--2182; *Angew. Chem.* **2012**, *124*, 2220--2224</jnl>.

<lit154><lit_a><jnl>H. Chen, S. Schlecht, T.^^C. Semple, J.^^F. Hartwig, *Science* **2000**, *287*, 1995--1997</jnl>; <lit_b><jnl>T. Ishiyama, J. Takagi, K. Ishida, N. Miyaura, N.^^R. Anastasi, J.^^F. Hartwig, *J. Am. Chem. Soc.* **2002**, *124*, 390--391</jnl>; <lit_c><jnl>J.^^F. Hartwig, *Acc. Chem. Res.* **2012**, *45*, 864--873</jnl>.

<lit155><lit_a><jnl>H.^^J. Davis, M.^^T. Mihai, R.^^J. Phipps, *J. Am. Chem. Soc.* **2016**, *138*, 12759--12762</jnl>; <lit_b><jnl>M.^^T. Mihai, H.^^J. Davis, G.^^R. Genov, R.^^J. Phipps, *ACS Catal.* **2018**, *8*, 3764--3769</jnl>; <lit_c><jnl>B. Lee, M.^^T. Mihai, V. Stojalnikova, R.^^J. Phipps, *J. Org. Chem.* **2019**, *84*, 13124--13134</jnl>.

<lit156><jnl>H.^^J. Davis, G.^^R. Genov, R.^^J. Phipps, *Angew. Chem. Int. Ed.* **2017**, *56*, 13351--13355; *Angew. Chem.* **2017**, *129*, 13536--13540</jnl>.

<lit157><jnl>G.^^R. Genov, J.^^L. Douthwaite, A.^^S.^^K. Lahdenperä, D.^^C. Gibson, R.^^J. Phipps, *Science* **2020**, *367*, 1246--1251</jnl>.

<lit158><lit_a><jnl>M.^^E. Hoque, R. Bisht, C. Haldar, B. Chattopadhyay, *J. Am. Chem. Soc.* **2017**, *139*, 7745--7748</jnl>; <lit_b><jnl>R. Bisht, M.^^E. Hoque, B.

Chattopadhyay, *Angew. Chem. Int. Ed.* **2018**, *57*, 15762--15766; *Angew. Chem.* **2018**, *130*, 15988--15992</jnl>.

<lit159><jnl>B. Chattopadhyay, J.^^E. Dannatt, I.^^L. Andujar-De^^Sanctis, K.^^A. Gore, R.^^E. Maleczka^^Jr., D.^^A. Singleton, M.^^R. Smith^^III, *J. Am. Chem. Soc.* **2017**, *139*, 7864--7871</jnl>.

<lit160><jnl>J. Chaturvedi, C. Haldar, R. Bisht, G. Pandey, B. Chattopadhyay, *J. Am. Chem. Soc.* **2021**, *143*, 7604--7611</jnl>.

<lit161><lit_a><jnl>W.^^A. Golding, R. Pierce-Higgins, R.^^J. Phipps, *J. Am. Chem. Soc.* **2018**, *140*, 13570--13574</jnl>; <lit_b><jnl>W.^^A. Golding, R.^^J. Phipps, *Chem. Sci.* **2020**, *11*, 3022--3027</jnl>; <lit_c><jnl>W.^^A. Golding, H.^^L. Schmitt, R.^^J. Phipps, *J. Am. Chem. Soc.* **2020**, *142*, 21891--21898</jnl>.

<lit162><lit_a><jnl>P.^^C. Roosen, V.^^A. Kallepalli, B. Chattopadhyay, D.^^A. Singleton, R.^^E. Maleczka, Jr., M.^^R. Smith^^III, *J. Am. Chem. Soc.* **2012**, *134*, 11350--11353</jnl>; <lit_b><jnl>S.^^M. Preshlock, D.^^L. Plattner, P.^^E. Maligres, S.^^W. Krska, R.^^E. Maleczka, Jr., M.^^R. Smith^^III*, Angew. Chem. Int. Ed.* **2013**, *52*, 12915--12919; *Angew. Chem.* **2013**, *125*, 13153--13157</jnl>; <lit_c><jnl>M.^^R. Smith^^III, R. Bisht, C. Haldar, G. Pandey, J.^^E. Dannatt, B. Ghaffari, R.^^E. Maleczka, Jr., B. Chattopadhyay, *ACS Catal.* **2018**, *8*, 6216--6223</jnl>.

<lit163><jnl>J. Zeng, M. Naito, T. Torigoe, M. Yamanaka, Y. Kuninobu, *Org. Lett.* **2020**, *22*, 3485--3489</jnl>.

<lit164><lit_a><jnl>Y. Kuninobu, H. Ida, M. Nishi, M. Kanai, *Nat. Chem.* **2015**, *7*, 712--717</jnl>; <lit_b><jnl>X. Lu, Y. Yoshigoe, H. Ida, M. Nishi, M. Kanai, Y. Kuninobu, *ACS Catal.* **2019**, *9*, 1705--1709</jnl>; <lit_c><jnl>J. Wang, T. Torigoe, Y. Kuninobu, *Org. Lett.* **2019**, *21*, 1342--1346</jnl>.

<lit165><jnl>R.^^L. Reyes, M. Sato, T. Iwai, K. Suzuki, S. Maeda, M. Sawamura, *Science* **2020**, *369*, 970--974</jnl>.

<lit166><jnl>D. Jiang, P. Tang, Q. Tan, Z. Yang, L. He, M. Zhang, *Chem. Eur. J.* **2020**, *26*, 15830--15834</jnl>.

<lit167><lit_a><jnl>Z. Zhang, K. Tanaka, J.-Q. Yu, *Nature* **2017**, *543*, 538--542</jnl>; <lit_b><jnl>T.^^K. Achar, K. Ramakrishna, T. Pal, S. Porey, P. Dolui, J.^^P. Biswas, D. Maiti, *Chem. Eur. J.* **2018**, *24*, 17906--17910</jnl>; <lit_c><jnl>T.^^K. Achar, J.^^P. Biswas, S. Porey, T. Pal, K. Ramakrishna, S. Maiti, D. Maiti, *J. Org. Chem.* **2019**, *84*, 8315--8321</jnl>; <lit_d><jnl>K. Ramakrishna, J.^^P. Biswas, S. Jana, T.^^K. Achar, S. Porey, D. Maiti, *Angew. Chem. Int. Ed.* **2019**, *58*, 13808--13812; *Angew. Chem.* **2019**, *131*, 13946--13950</jnl>; <lit_e><jnl>H. Shi, Y. Lu, J. Weng, K.^^L. Bay, X. Chen, K. Tanaka, P. Verma, K.^^N. Houk, J.-Q. Yu, *Nat. Chem.* **2020**, *12*, 399--404</jnl>.

<lit168><jnl>H.^^L. Li, Y. Kuninobu, M. Kanai, *Angew. Chem. Int. Ed.* **2017**, *56*, 1495--1499; *Angew. Chem.* **2017**, *129*, 1517--1521</jnl>.

<lit169><jnl>L. Yang, N. Uemura, Y. Nakao, *J. Am. Chem. Soc.* **2019**, *141*, 7972--7979</jnl>.

<lit170><jnl>J. Trouvé, P. Zardi, S. Al-Shehimy, T. Roisnel, R. Gramage-Doria, *Angew. Chem. Int. Ed.* **2021**, *60*, 18006--18013; *Angew. Chem.* **2021**, *133*, 18154--18161</jnl>.

<lit171><jnl>N. Hara, N. Uemura, Y. Nakao, *Chem. Commun.* **2021**, *57*, 5957--5960</jnl>.

<lit172><lit_a><jnl>R.-H. Wang, J.-F. Li, Y. Li, S.-L. Qi, T. Zhang, Y.-X. Luan, M. Ye, *ACS Catal.* **2021**, *11*, 858--864</jnl>; <lit_b><jnl>G. Yin, Y. Li, R.-H. Wang, J.-F. Li, X.-T. Xu, Y.-X. Luan, M. Ye, *ACS Catal.* **2021**, *11*, 4606--4612</jnl>.

<lit173><jnl>M. Catellani, F. Frignani, A. Rangoni, *Angew. Chem. Int. Ed.* **1997**, *36*, 119--122; *Angew. Chem.* **1997**, *109*, 142--145</jnl>.

<lit174><jnl>X.-C. Wang, W. Gong, L.-Z. Fang, R.-Y. Zhu, S. Li, K.^^M. Engle, J.-Q. Yu, *Nature* **2015**, *519*, 334--338</jnl>.

<lit175><lit_a><jnl>P.-X. Shen, X.-C. Wang, P. Wang, R.-Y. Zhu, J.-Q. Yu, *J. Am. Chem. Soc.* **2015**, *137*, 11574--11577</jnl>; <lit_b><other>J.-Q. Yu (The Scripps Research Institute), WO 123361, **2016**</other>.

<lit176><jnl>Z. Dong, J. Wang, G. Dong, *J. Am. Chem. Soc.* **2015**, *137*, 5887--5890</jnl>.

<lit177><jnl>P. Wang, M.^^E. Farmer, X. Huo, P. Jain, P.-X. Shen, M. Ishoey, J.^^E. Bradner, S.^^R. Wisniewski, M.^^D. Eastgate, J.-Q. Yu, *J. Am. Chem. Soc.* **2016**, *138*, 9269--9276</jnl>.

<lit178><jnl>P. Wang, M.^^E. Farmer, J.-Q. Yu, *Angew. Chem. Int. Ed.* **2017**, *56*, 5125--5129; *Angew. Chem.* **2017**, *129*, 5207--5211</jnl>.

<lit179><jnl>J. Liu, Q. Ding, W. Fang, W. Wu, Y. Zhang, Y. Peng, *J. Org. Chem.* **2018**, *83*, 13211--13216</jnl>.

<lit180><jnl>J. Han, L. Zhang, Y. Zhu, Y. Zheng, X. Chen, Z.-B. Huang, D.-Q. Shi, Y. Zhao, *Chem. Commun.* **2016**, *52*, 6903--6906</jnl>.

<lit181><jnl>Q. Ding, S. Ye, G. Cheng, P. Wang, M.^^E. Farmer, J.-Q. Yu, *J. Am. Chem. Soc.* **2017**, *139*, 417--425</jnl>.

<lit182><jnl>P.-X. Ling, K. Chen, B.-F. Shi, *Chem. Commun.* **2017**, *53*, 2166--2169</jnl>.

<lit183><jnl>G.-C. Li, P. Wang, M.^^E. Farmer, J.-Q. Yu, *Angew. Chem. Int. Ed.* **2017**, *56*, 6874--6877; *Angew. Chem.* **2017**, *129*, 6978--6981</jnl>.

<lit184><jnl>G. Cheng, P. Wang, J.-Q. Yu, *Angew. Chem. Int. Ed.* **2017**, *56*, 8183--8186; *Angew. Chem.* **2017**, *129*, 8295--8298</jnl>.

<lit185><jnl>Q. Li, E.^^M. Ferreira, *Chem. Eur. J.* **2017**, *23*, 11519--11523</jnl>.

<lit186><jnl>M.^^E. Farmer, P. Wang, H. Shi, J.-Q. Yu, *ACS Catal.* **2018**, *8*, 7362--7367</jnl>.

<lit187><jnl>L.-Y. Liu, J.^^X. Qiao, K.-S. Yeung, W.^^R. Ewing, J.-Q. Yu, *Angew. Chem. Int. Ed.* **2020**, *59*, 13831--13835; *Angew. Chem.* **2020**, *132*, 13935--13939</jnl>.

<lit188><lit_a><jnl>L.-Y. Liu, J.^^X. Qiao, K.-S. Yeung, W.^^R. Ewing, J.-Q. Yu, *J. Am. Chem. Soc.* **2019**, *141*, 14870--14877</jnl>; <lit_b><jnl>X. Ma, X. Zhao, R. Zhu, D. Zhang, *J. Org. Chem.* **2020**, *85*, 5995--6007</jnl>.

<lit189><lit_a><jnl>H. Shi, A.^^N. Herron, Y. Shao, Q. Shao, J.-Q. Yu, *Nature* **2018**, *558*, 581--586</jnl>; <lit_b><jnl>D.^^E. Hill, J.-Q. Yu, D.^^G. Blackmond, *J. Org. Chem.* **2020**, *85*, 13674--13879</jnl>; <lit_c><jnl>F. Jia, J. Luo, B. Zhang, *Adv. Synth. Catal.* **2020**, *362*, 1686--1695</jnl>.

<lit190><jnl>U. Dutta, S. Porey, S. Pimparkar, A. Mandal, J. Grover, A. Koodan, D. Maiti, *Angew. Chem. Int. Ed.* **2020**, *59*, 20831--20836; *Angew. Chem.* **2020**, *132*, 21017--21022</jnl>.

<lit191><lit_a><jnl>P. Wang, G.-C. Li, P. Jain, M.^^E. Farmer, J. He, P.-X. Shen, J.-Q. Yu, *J. Am. Chem. Soc.* **2016**, *138*, 14092--14099</jnl>; <lit_b><jnl>H. Shi, P. Wang, S. Suzuki, M.^^E. Farmer, J.-Q. Yu, *J. Am. Chem. Soc.* **2016**, *138*, 14876--14879</jnl>.

<lit192><jnl>Z. Wu, N. Fatuzzo, G. Dong, *J. Am. Chem. Soc.* **2020**, *142*, 2715--2720</jnl>.

<lit193><lit_a><jnl>A.^^H. Sandtorv, *Adv. Synth. Catal.* **2015**, *357*, 2403--2435</jnl>; <lit_b><jnl>M. Wegmann, M. Henkel, T. Bach, *Org. Biomol. Chem.* **2018**, *16*, 5376--

5385</jnl>; <lit_c><jnl>B. Deka, M.^^L. Deb, P.^^K. Baruah, *Top. Curr. Chem.* **2020**, *378*, 22--54</jnl>.

<lit194><lit_a><jnl>L. Jiao, T. Bach, *J. Am. Chem. Soc.* **2011**, *133*, 12990--12993</jnl>; <lit_b><jnl>L. Jiao, E. Herdtweck, T. Bach, *J. Am. Chem. Soc.* **2012**, *134*, 14563--14572</jnl>; <lit_c><jnl>H.^^K. Potukuchi, T. Bach, *J. Org. Chem.* **2013**, *78*, 12263--12267</jnl>; <lit_d><jnl>L. Jiao, T. Bach, *Angew. Chem. Int. Ed.* **2013**, *52*, 6080--6083; *Angew. Chem.* **2013**, *125*, 6196--6199</jnl>; <lit_e><jnl>L. Jiao, T. Bach, *Synthesis* **2014**, *46*, 35--41</jnl>.

<lit195><lit_a><jnl>M. Henkel, T. Bach, *Synthesis* **2020**, *52*, 1231--1238</jnl>; <lit_b><jnl>Y. Gao, J. Li, S. Bai, D. Tu, C. Yang, Z. Ye, B. Hu, X. Qi, C. Jiang, *Org. Chem. Front.* **2020**, *7*, 1149--1157</jnl>.

<lit196>For selected examples, see: <lit_a><jnl>M. Nuth, H. Guan, N. Zhukovkaya, Y.^^L. Saw, R.^^P. Ricciardi, *J. Med. Chem.* **2013**, *56*, 3235—3246</jnl>; <lit_b><jnl>M. Mizutani, S. Yasusa, C. Mukai, *Chem. Commun.* **2014**, *50*, 5782--5785</jnl>; <lit_c><jnl>S.-Z. Jiang, X.-Y. Zeng, X. Liang, T. Lei, K. Wei, Y.-R. Yang, *Angew. Chem. Int. Ed.* **2016**, *55*, 4044--4048; *Angew. Chem.* **2016**, *128*, 4112--4116</jnl>; <lit_d><jnl>R.^^A. Denny, A.^^C. Flick, J. Coe, J. Langille, A. Basak, S. Liu, I. Stock, P. Sahasrabudhe, P. Bonin, D.^^A. Hay, P.^^E. Brennan, M. Pletcher, L.^^H. Jones, E.^^L. Piatnitski^^Chekler, *J. Med. Chem.* **2017**, *60*, 5349--5363</jnl>; <lit_e><jnl>T. Xiao, Z.-T. Chen, L.-F. Deng, D. Zhang, X.-Y. Liu, H. Song, Y. Qin, *Chem. Commun.* **2017**, *53*, 12665--12667</jnl>.

<lit197><jnl>H. Zhang, H.-Y. Wang, Y. Luo, C. Chen, Y. Cao, P. Chen, Y.-L. Guo, Y. Lan, G. Liu, *ACS Catal.* **2018**, *8*, 2173--2180</jnl>.

<lit198><jnl>Y. Niu, P.-B. Bai, Q.-X. Lou, S.-D. Yang, *ChemCatChem* **2020**, *12*, 3644--3649</jnl>.

<lit199><jnl>Y. Gao, W. Zhu, L. Yin, B. Dong, J. Fu, Z. Ye, F. Xue, C. Jiang, *Tetrahedron Lett.* **2017**, *58*, 2213--2216</jnl>.

<lit200><jnl>Y. Mohr, M. Renom-Carrasco, C. Dermarcy, E.^^A. Quadrelli, C. Camp, F.^^M. Wisser, E. Clot, C. Thieuleux, J. Canivet, *ACS Catal.* **2020**, *10*, 2713--1719</jnl>.

Scheme^^1 a) Classical directing group strategy for the functionalization of C<C->H bonds; b) Transient directing group strategy. DG: Directing Group, TM: Transition-Metal, FG: Functional Group.

Scheme^^2 *ortho*-Arylation of phenols and naphthol with aryl halides.

Scheme^^3 *ortho*-Arylation of BINOLs with aryl halides.

Scheme^^4 *ortho*-Alkylation of phenols and aniline with unactivated alkenes.

Scheme^^5 Hydroformylation of homoallylic alcohols.

Scheme^^6 Hydroformylation and subsequent oxidation of alkenes bearing a hydroxy group.

Scheme^^7 Hydroformylation and subsequent oxidation of homoallylic alcohols with scaffolding-ligand to γ-lactones.

Scheme^^8 Hydroformylation and subsequent oxidation of homoallylic alcohols with scaffolding-ligand to δ-lactones.

Scheme^^9 Hydroformylation of allylic alcohols and sulfonamides to aldehydes and carboxylic acids.

Scheme^^10 Enantioselective hydroformylation and subsequent reduction of allylic amines and anilines to chiral γ-aminoalcohols.

Scheme^^23 Annulation of benzaldehydes and aryl iodides towards fluorenones through double Pd-catalyzed transient imine-directed C<C->H functionalization.

Scheme^^24 Annulation of benzaldehydes and arenes towards fluorenones through double Pd-catalyzed transient imine-directed C<C->H functionalization.

Scheme^^25 Dehydrogenative *ortho*-arylation of benzaldehydes with arenes using α-methylalanine as transient directing mediator.

Scheme^^26 Dehydrogenative *ortho*-heteroarylation of benzaldehydes with heteroarenes and benzylamine.

Scheme^^27 First examples of alkylation of aromatic aldehydes and ketones using transient imine-directing groups.

Scheme^^28 (Enantioselective) intramolecular Rh- and Ru-catalyzed formation of indolines and 2,3-dihydrofurans using the transient imine directing group strategy with (chiral) amines.

Scheme^^29 *ortho*-Alkylation of benzaldehydes with *N*-alkyl-maleimides through a transient imine directing group strategy with substituted aniline.

Scheme^^30 *ortho*-Alkylations of benzaldehydes with potassium alkyl trifluoroborates via transient imine directing group strategy.

Scheme^^31 Atroposelective Pd-catalyzed allylation of biaryls with allylic esters or carbonates using L-*tert*-leucine as chiral transient directing mediator.

Scheme^^32 *ortho*-Olefination of (hetero)aromatic aldehydes with activated alkenes through rhodium-catalyzed transient imine directing strategy with tosylamide.

Scheme^^33 Remote δ-C($sp^2$)<C->H olefination of β-aryl substituted aliphatic aldehydes with activated alkenes using an enamine directing group.

Scheme^^34 Remote C($sp^2$)<C->H olefination of biaryls aldehydes and amines with activated alkenes through a Pd-catalyzed transient imine directing group strategy.

Scheme^^35 Atroposelective Pd-catalyzed C($sp^2$)<C->H olefination of biaryl aldehydes with acrylates and styrenes using L-*tert*-leucine transient directing mediator.

Scheme^^36 Key transient imine-directed C($sp^2$)<C->H olefination of a biaryl aldehyde intermediate with butyl acrylate for the total synthesis of TAN-1085.

Scheme^^37 Enantioselective palladaelectro-catalyzed transient imine-directed olefination of biaryl aldehydes with L-*tert*-leucine as transient directing mediator.

Scheme^^38 C-4-*ortho*-olefination of indole-3-carbaldehydes through Pd-catalyzed transient imine directing strategy with glycine.

Scheme^^39 Rh-catalyzed synthesis of indoles from anilines and alkynes via the formation of a transient nitrosamine directing group.

Scheme^^40 Enantioselective Pd-catalyzed alkynylation of bi(hetero)aromatic aldehydes using L-*tert*-leucine as transient directing mediator.

Scheme^^41 Rh-catalyzed alkynylation of benzaldehydes using an aniline transient directing mediator.

Scheme^^42 *ortho*-Amidation of benzaldehydes with sulfonyl azides through transient imine directing strategy with anilines.

Scheme^^43 Proposed mechanism for the Ir- or Ru- catalyzed transient imine-directed *ortho*-amidation of benzaldehydes with sulfonyl azides and anilines as transient directing mediator.

Scheme^^44 *ortho*-Amidation of benzaldehydes and aromatic ketones with dioxazolones through transient imine directing strategy.

Scheme^^45 Proposed shared mechanism for the Rh- or Co- catalyzed transient imine-directed *ortho*-amidation of benzaldehydes and aromatic ketones with dioxazolones and anilines as transient directing mediators.

Scheme^^46 Transient imine directing strategy for the synthesis of an unsymmetrical urea and *ortho*-imidated benzaldehydes using anilines as transient directing mediators.

Scheme^^47 Rh-catalyzed annulation of aldehydes with nitrosoarenes through transient imine-directed *ortho*-amination with benzylamines as transient directing mediators.

Scheme^^48 Pd-catalyzed *ortho*-halogenation of benzaldehydes with *N*-chloro and *N*-bromosuccinimide through the transient imine directing strategy with anthranilic acids as transient directing mediators.

Scheme^^49 Pd-catalyzed *ortho*-halogenation of benzaldehydes with *N*-chloro and *N*-bromosuccinimide through transient imine directing strategy employing trifluoromethylanilines as transient directing mediators.

Scheme^^50 Pd-catalyzed *ortho*-Fluorinations of benzaldehydes and aromatic ketones with 1-fluoro-2,4,6-trimethylpyridinium triflate or NFSI using transient directing groups employing aniline-2,4-disulfonic acid or methyl carbamate.

Scheme^^51 Pd-catalyzed *ortho*-hydroxylation of benzaldehydes with *p*-TsOH through transient imine directing strategy with 4-chloroanthranilic acid as the transient directing mediator.

Scheme^^52 Pd-catalyzed *ortho*-methoxylation of benzaldehydes with methanol and potassium persulfate through transient imine directing strategy with 4-trifluoromethylaniline transient directing group.

Scheme^^53 Ir-catalyzed o*rtho*- and *meta*-borylation of benzaldehydes with $B_2Pin_2$ through transient imine directing strategy with primary amines.

Scheme^^54 Pd-catalyzed *ortho*-selenylation of benzaldehydes with diaryl diselenides through transient imine directing strategy with benzidine.

Scheme^^55 Pd-catalyzed *ortho*-silylation of benzaldehydes with hexamethyldisilane via transient imine directing strategy with a β-aminoacid.

Scheme^^56 Pd-catalyzed *ortho*-deuteration of benzaldehydes through transient imine directing strategy with *n*-butylamine.

Scheme^^57 Rh-catalyzed alkylation of (*E*)-4-phenylbut-3-en-2-one with unactivated terminal alkenes through transient enamine directing strategy with diethylamine.

Scheme^^58 Ir-catalyzed alkylation of α,β-unsaturated aldehydes with potassium butyltrifluoroborate using an imine transient directing group.

Scheme^^59 Pd-catalyzed (enantioselective) benzyclic C<C->H (hetero)arylation of *ortho*-alkyl benzaldehydes using a transient directing group.

Scheme^^60 Pd-catalyzed benzylic C<C->H (hetero)arylation of 3-alkyl-2-(hetero)arene carbaldehydes using a transient directing group.

Scheme^^61 Proposed shared mechanism for the benzylic C($sp^3$)<C->H (hetero)arylation of 3-alkyl-2-(hetero)arene carbaldehydes using transient imine directing groups employing various amine derivatives.

Scheme^^62 Pd-catalyzed β-arylation of aliphatic aldehydes using imine transient directing groups.

Scheme^^63 Pd-catalyzed β-arylation of aliphatic aldehydes using imine transient directing groups.

Scheme^^64 Pd-catalyzed γ-arylation of aliphatic aldehydes using an imine transient directing group with L-phenylalanine as transient directing mediator.

Scheme^^65 Pioneering reports for the Pd-catalyzed β-arylation of aliphatic ketones using imine transient directing groups with α- and β- aminoacids as transient directing mediators.

Scheme^^66 Pd-catalyzed β-arylation of aliphatic ketones using imine transient directing groups.

Scheme^^67 Pd-catalyzed dehydrogenative β-arylation of aliphatic aldehydes using an imine transient directing group with β-alanine as the transient directing mediator.

Scheme^^68 Rh-catalyzed α-ethylation of cyclopentanones using an enamine transient directing group with pyrrolidinopyridine as the transient directing mediator.

Scheme^^69 Ir- and Rh- catalyzed alkylation and alkenylation of aliphatic ketones using a transient enamine or imine directing group.

Scheme^^70 Enantioselective Pd-catalyzed benzylic fluorination of *ortho*-alkylbenzaldehydes using a chiral transient imine directing group employing L-*tert*-leucine diethylamide as transient directing mediator.

Scheme^^71 $C(sp^3)$<C->O bond formation in aldehydes and ketones using a transient imine directing group with acetylhydrazine as the transient directing mediator.

Scheme^^72 Pioneering reports on the Pd-catalyzed γ-arylation of aliphatic amines using transient imine directing groups employing aldehyde transient directing mediators.

Scheme^^73 Pd-catalyzed γ-arylation of aliphatic amines or amino esters using imine transient directing groups employing aldehyde or acetal transient directing mediators.

Scheme^^74 Proposed shared mechanism for the $C(sp^3)$<C->H (hetero)arylation of aliphatic amines using transient imine directing groups employing various aldehyde derivatives.

Scheme^^75 Pd-catalyzed γ- and δ- (hetero)arylation of aliphatic amines using transient imine directing groups with a substituted benzaldehyde or phenyl-2-oxoacetic acid as transient directing mediators.

Scheme^^76 Pd-catalyzed γ-fluorination of aliphatic amines using a transient directing group derived from 2-hydroxynicotinaldehyde and proposed mechanism of the methylene fluorination.

Scheme^^77 Pd-catalyzed β- and γ-oxidation of aliphatic amines using a transient directing group derived from salicylaldehyde and 2-hydroxynicotinaldehyde.

Scheme^^78 Rh-catalyzed transalkylation of aliphatic ketones using a transient imine directing group derived from 2-amino-3-picoline.

Scheme^^79 Intra- and inter- molecular Rh-catalyzed C<C->C bond functionalization of aliphatic ketones and indanones using a transient imine directing group derived from 2-aminopryridine.

Scheme^^80 Intramolecular Rh-catalyzed C<C->C bond functionalization of cyclic ketones using transient imine directing groups derived from 2-aminopryiridines.

Scheme^^81 Rh-catalyzed C<C->C bond functionalization of cyclic ketones using a transient imine directing group derived from 2-amino-3-picoline.

Scheme^^82 Rh-catalyzed carbonylative C<C->C bond activation of cyclopropylamines via the formation of a transient (thio)urea directing group employing iso(thio)cyanates.

Scheme^^83 Pd-catalyzed arylation of aliphatic and benzylic amines using the transient formation of carbamates with $CO_2$.

Scheme^^84 Pd- and Ru- catalyzed C($sp^2$)<C->H arylation and alkenylation of various arenes using the transient formation of benzoic acids with $CO_2$.

Scheme^^85 Electrostatically directed Rh-catalyzed hydroformylation and reduction of unsaturated carboxylic acids employing a triarylphosphine/guanidine bifunctional transient directing mediator.

Scheme^^86 Ir-catalyzed, electrostatically directed *meta*-selective borylations of ammonium and phosphonium salts, and amides bearing a remote aryl moiety with a bipyridine/ammonium sulfonate bifunctional transient directing mediator.

Scheme^^87 Enantioselective Ir-catalyzed, electrostatically directed *meta*-selective borylation of amide and aminophosphine oxide through desymmetrization with a bipyridine/chiral ammonium sulfonate bifunctional transient directing mediator.

Scheme^^88 Ir-catalyzed, electrostatically directed *para*- and *meta*- selective borylations of aromatic esters and amides with a bipyridine/quinolinone bifunctional transient directing mediator.

Scheme^^89 Ir-catalyzed, electrostatically directed *ortho*-selective borylation of phenols.

Scheme^^90 Pd-catalyzed, electrostatically directed *meta*-selective functionalization of aryldichlorides with ammonium or sodium sulfonated biarylphosphine ligands as transient directing mediator.

Scheme^^91 Ir-catalyzed, *ortho*-selective borylation of anilines directed by hydrogen bonds.

Scheme^^92 Ir-catalyzed, *ortho*-selective borylation of aromatic thioethers directed by hydrogen bonds.

Scheme^^93 Ir-catalyzed, *meta*-selective borylation of aromatic amides and phosphine oxides directed by a hydrogen-bonded transient directing group based on a urea/bipyridine bifunctional system.

Scheme^^94 Enantioselective Ir-catalyzed borylation of aliphatic amides and esters directed by a hydrogen-bonded transient directing group based on a urea/pyridine bifunctional system.

Scheme^^106 *meta*-Selective C($sp^2$)<C->H arylation of electron-rich arenes promoted by a dual ligand system and Pd/norbornene cooperative catalysis.

Scheme^^107 *meta*-Selective C($sp^2$)<C->H amination, alkynylation and chlorination of anilines and phenols through Pd/norbornene cooperative catalysis.

Scheme^^108 Distal C($sp^2$)<C->H alkene arylation and alkylation through Pd/norbornene cooperative catalysis.

Scheme^^109 C2-selective alkylation of indoles and pyrroles with alkyl bromides through Pd/norbornene cooperative catalysis.

Scheme^^110 General mechanism for the C2-selective functionalization of indoles and pyrroles through Pd/norbornene cooperative catalysis.

Scheme^^111 C2-selective arylation of indoles with iodoarenes through Pd/norbornene cooperative catalysis.

Scheme^^112 Ligand-free, Pd-catalyzed C3-selective arylation of indoles using LiHMDS as both a base and a transient directing group.

*Clément Jacob was born in Saint-Etienne, France in 1993 and studied chemistry at the Ecole Nationale Supérieure de Chimie de Montpellier. After several industrial stays at Janssen Pharmaceutica and Syngenta, he obtained his master thesis in 2018 focusing on the synthesis of novel bioactive heterocycles for the agrochemical industry. He then moved to Belgium to start his joint Ph.D. studies at the Université libre de Bruxelles and the University of Antwerp under the supervision of Prof. Gwilherm Evano and Prof. Bert Maes as an EOS fellow, focusing on C-H bonds functionalization using transient directing groups.<memr1>*

*Prof. Bert U.W. Maes obtained his Ph.D. in Organic Chemistry at UAntwerp and subsequently received a Post-Doctoral Fellowship of the Research Foundation (FWO) in Flanders (Belgium). He worked at the École Normale Supérieure in Paris with Prof. Anny Jutand (CNRS) studying the reaction mechanism of palladium-catalyzed cross-coupling reactions. In 2003 Maes was appointed Assistant Professor in the Department of Chemistry at UAntwerp and currently is Full Professor. In 2019 he was awarded a Collen-Francqui*

*Research Professorship by the Francqui Foundation. His research focuses on strong bond activation with homogeneous catalysis, renewables, C1 reactants, heterocyclic and sustainable chemistry. He is spokesman of CASCH, an Excellence Center of UAntwerp.* *<memr2>*

*Prof. Gwilherm Evano studied chemistry at the Ecole Normale Supérieure in Paris and received his Ph.D. from the Université Pierre et Marie Curie in 2002 under the supervision of Prof. François Couty and Prof. Claude Agami. After postdoctoral studies with Prof. James S. Panek at Boston University, he joined the CNRS as an associate professor in 2004. He then moved to the Université libre de Bruxelles, where he became the head of the Laboratory of Organic Chemistry in 2012. His research focuses on natural/bioactive product synthesis, copper catalysis, photoredox catalysis, organometallic chemistry, and on the chemistry of heteroatom-substituted alkynes and reactive intermediates.<memr3>*