Journal Name

REVIEW

Transient Imines as 'Next Generation' Directing Groups for the Catalytic Functionalisation of C–H Bonds in a Single Operation

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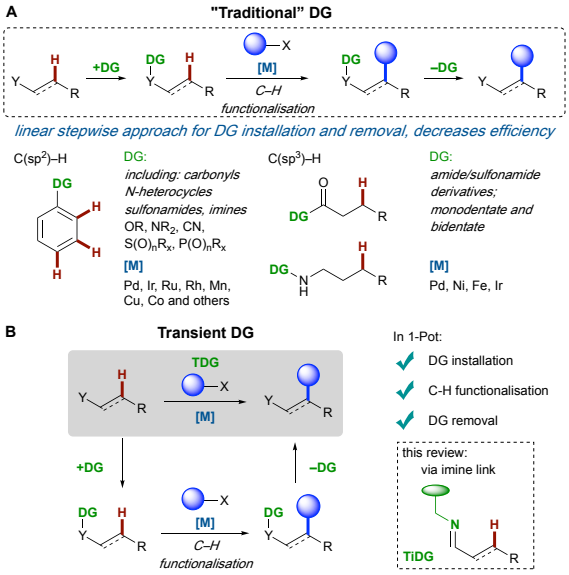
C–H Functionalisation promises a paradigm shift in synthetic planning. However, the additional steps often required to install and remove directing groups currently detracts from the efficiency. The strategy of reversible installation of a directing group via an imine linkage has recently emerged, with the imine formed and hydrolysed *in situ*. Such transient directing groups can promote transition metal catalysed functionalisation of unactivated C–H bonds of aldehydes, ketones and amines. This approach removes additional steps usually required for covalent directing groups and can use catalytic quantities of the imine forming component. This review updates the rapidly developing field of transient directing groups for C–H functionalisation on sp^2 and sp^3 carbon centres, to form new C–C and C–X bonds. We focus on the structures of the transient directing groups as mono or bidentate coordinating groups for various metal catalysts.

1. Introduction

The use of transition metal catalysts to exploit unreactive C–H bonds as hidden reactive centres has the potential to revolutionise organic synthesis.[1] In lieu of pre-installed reactive handles, this approach can provide simplification of synthetic routes, new disconnections, and new synthetic starting points. The inherent reactivity of certain C–H bonds with regard to steric and electronic environment can allow their selective functionalisation with electrophilic reagents.[2] However, to date, the challenge of predictable regiocontrol is most reliably addressed through the use of directing groups (Scheme 1A).[3-5] Directing groups (DGs) are Lewis basic sites that coordinate the catalyst and locate the metal centre at a suitable distance from a selected C–H bond to allow 'activation' to occur. From the resulting C–M bond, productive C–C or C–X bond formation can then be effected, with regeneration of the metal catalyst. This strategy has been successful for both aromatic[4] and aliphatic[5] substrates through various mechanisms.[3-6] For C(sp^2)–H bond functionalisation, numerous coordinating groups have been successfully employed to promote reaction at the *ortho*-position using various metal catalysts.[4] Furthermore, designer systems have been successful in achieving selective functionalisation of C–H bonds at positions *meta*-[7] and *para*- to the DG.[8] For C(sp^3)–H bonds, pyridine or amide directing groups have been used effectively, as well as oximes.[5,9] In 2005, Daugulis first presented the use of the popular bidentate 8-aminoquinoline amide for the β-arylation of carboxylic acid derivatives using palladium catalysis.[9a,10] Yu has developed highly effective mono-coordinating amide DGs along with ligands to promote palladium catalysed C–H functionalisation reactions.[11] Developments in both sp^2 and sp^3 systems have focused on more easily removed DG classes.[12]



Scheme 1. Comparison of traditional and transient directing groups for C–H functionalisation

A crucial limitation to this directed strategy is the additional steps required to install and remove directing groups. Not only does this involve additional 'pre-functionalisation' steps to install the directing group, but the removal can itself require forcing conditions, limiting the use of complex substrates and late stage functionalisation strategies. These two additional steps may negate improvements in efficiency offered by a C–H functionalisation approach.[13] This review covers the concept of transient directing groups, to avoid the requirement for prefunctionalisation (Scheme 1B, and Figure 1 for overview). A transient DG will reversibly link to the substrate so that C–H functionalisation can occur and undergo cleavage all in one

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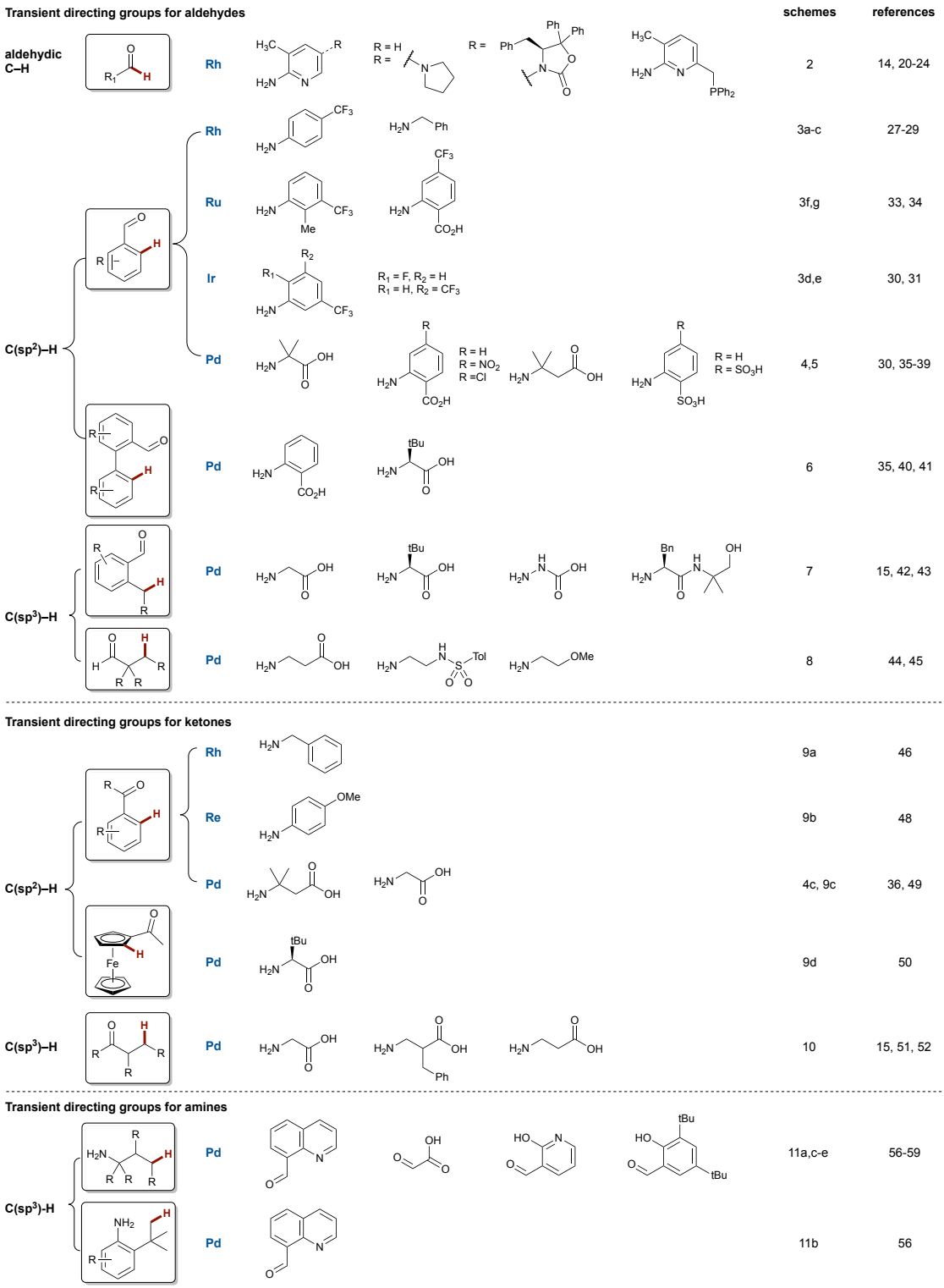

Figure 1: Summary of all transient imine directing groups for the functionalisation of C–H bonds.

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reaction pot. This enables the catalytic usage of the directing group precursor when the rates of the two catalytic cycles are compatible. The seminal report using this concept was from Jun in 1997, on the hydroacylation of alkenes with aldehydic C–H activation using 2-amino-3-picoline to form directing imines.[14] However, it is since Yu reported an amino acid as a transient imine DG for functionalisation of sp^3 C–H bonds with palladium in 2016,[15] that the field has seen rapid development. In recent months, other reviews on transient mediators have appeared.[16,17,18]

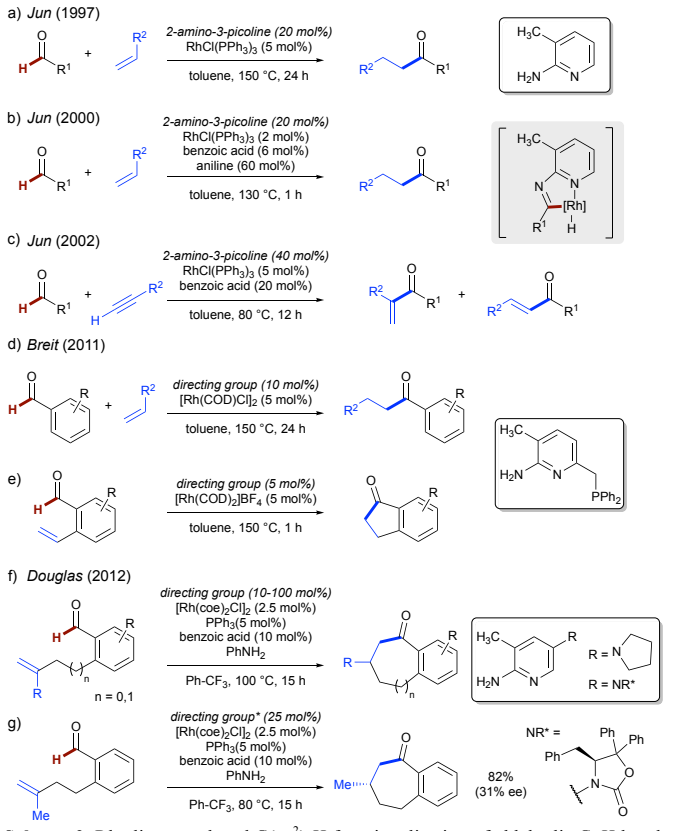
Here we focus specifically on transiently formed imines as directing groups (transient imine directing groups, "TiDGs"). The success of a catalytic transient directing group is reliant upon imine formation and hydrolysis, as well as suitable coordination properties to stabilize intermediates on the catalytic cycle. As such the structure of the TiDG is intimately related to the success of a reaction. Furthermore, the relative loading of catalytic metal and the catalytic additive to form the true directing group is important so both cycles can operate in sync. This review will bring the reader up to date in this fast-moving field, covering the literature up to and including March 2018. We will provide an overview of structural classes that have been used as transient directing groups for different substrates (Figure 1) with discussion of their applications. While the amine or aldehyde additives are themselves commonly referred to as 'transient directing groups' (TDG), and will be here also, it is given that the true directing group corresponds to the imine formed through amine-aldehyde condensation, which is itself transient. Generally, the imine-nitrogen provides the first metal coordinating site, along with second coordinating sites that may be designed into the directing group as required. The review is in 3 main parts covering the use of transient imine directing groups for functionalisation of aldehydes, ketones and amines. The review is ordered chronologically by substrate, metal catalyst, and transformation.

2. C–H Functionalisation of Aldehydes

Aldehydes are attractive substrates for C–H functionalisation with transient directing groups as they readily undergo reversible imine condensation, and provide common and valuable functional groups for further manipulations. Indeed, the catalytic use of amines with aldehydes is well known in the field of organocatalysis.[19] The very early work in the field of C–H functionalisation with transient directing groups explored functionalisation of aldehydic C–H bonds. More recently benzaldehydes have been explored with various metals for functionalisation of sp^2 and sp^3 C–H bonds at *ortho* (*beta*) and benzylic (*gamma*) positions, and at the 2' position of biaryls (*delta* functionalisation). Aliphatic aldehydes have been successfully employed as substrates for *beta*-arylation, using palladium catalysts.

2.1 Aldehydic C–H bonds

The first examples of C–H functionalisation using a transient imine directing group were pioneered by Jun. In the seminal example, a TiDG formed from the condensation of 2-amino-3-picoline with aldehydes facilitated the alkylation of aldehydic C–H bonds with alkenes using rhodium catalysis (Scheme 2a).[14] Imine formation enabled cyclometallation to occur by coordination of the pyridine nitrogen followed by activation of the aldehydic C–H. The resulting rhodacycle (see grey box, Scheme 2) effected hydrorhodation of the alkene, and reductive elimination gave the functionalised imine. *In-situ* hydrolysis furnished the product ketone, regenerating the 2-amino-3-picoline TDG.



Scheme 2. Rhodium catalysed C(sp^2)-H functionalisation of aldehydic C–H bonds using a transient imine directing group. TDGs boxed. Proposed metallacycles in grey box.

Good to excellent yields were reported with both aliphatic and aromatic aldehydes and alkenes (eg R^1 = Ph, R^2 = C_6F_5 90%

and R^1 = Cy, R^2 = C_3H_7 67%). Only sterically hindered pivaldehyde gave a low yield (6%) with 1-pentene. In the absence of 2-amino-3-picoline a decarbonylation product was formed exclusively. Jun then expanded the scope to include heterocyclic examples.[20] An improved catalytic system was achieved when benzoic acid and aniline additives were employed (Scheme 2b).[21] Mechanistic studies suggested that aniline accelerated the reaction by providing a transimination pathway (catalysed by benzoic acid) which was faster than the direct condensation of the aldehyde and 2-amino-3-picoline. Jun went on to show that when utilising alkyl-substituted alkynes as the coupling partner, hydroacylation of aldehydes afforded an isomeric mixture of α,β-unsaturated ketones (Scheme 2c).[22] Aromatic and heteroaromatic aldehydes afforded exclusively the branched product in excellent (66–95%) yields, however the linear *E*-α-β-enone product could be obtained exclusively with aliphatic aldehydes when using a bulky *tert*-butyl substituent on the alkyne.

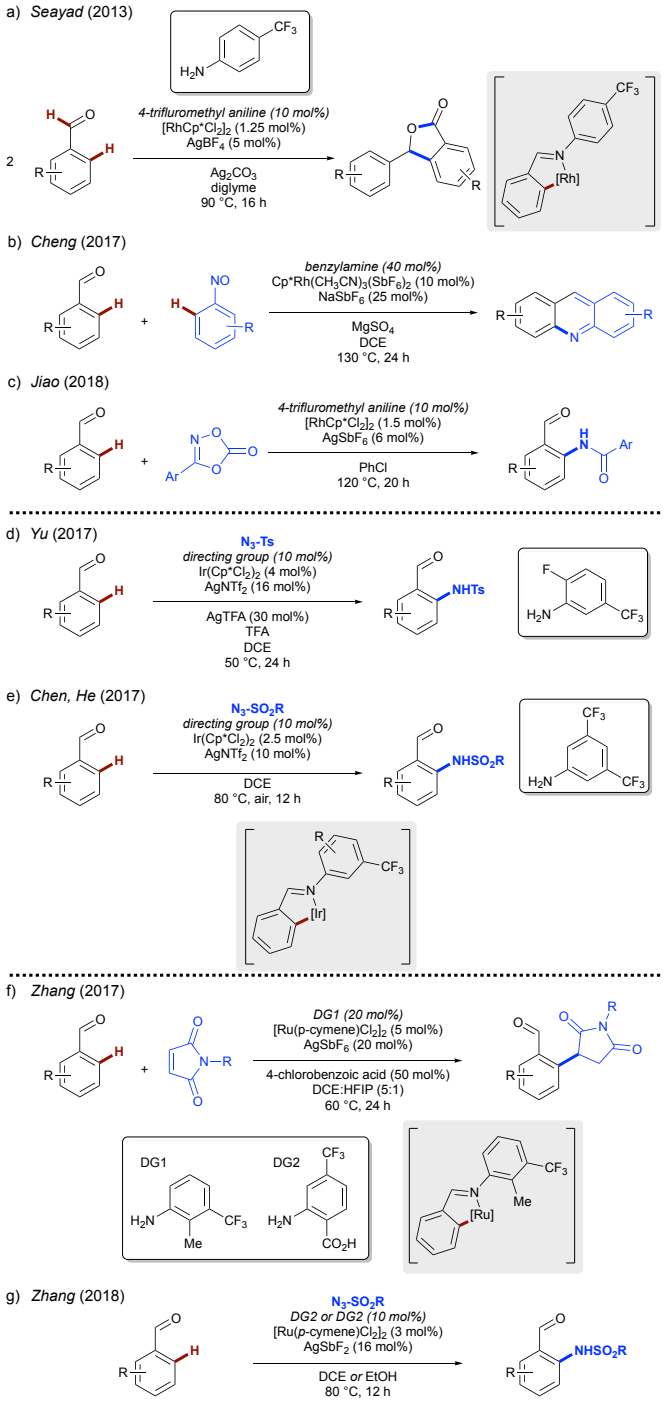
Breit developed an inter- and intramolecular hydroacylation of alkenes facilitated by a TiDG (Schemes 2d and 2e).[23] In this case, the 2-amino-3-picoline was decorated with a phosphine at the 6 position, to enhance the binding to the catalytically active rhodium centre, increasing the effective molarity and hence promoting the functionalisation of the aldehyde C–H. This modification made the addition of other additives unnecessary and lower loadings of the TDG possible, although the TDG itself required a 5-step synthesis. The methyl group in the 3 position was thought to assist in promoting the correct conformation of the imine. Both inter and intramolecular reactions displayed good functional group tolerance.

Douglas and coworkers developed another hydroacylation using a 2-amino-3-picoline-based TDG, functionalised at the 5-position by an amino or chiral cyclic carbamate group (Schemes 2f and 2g).[24] This method uses a terminal propyl or butyl alkene appended at the *ortho*-position of the aldehyde for 6- or 7-membered ring formation. In addition to the benzaldehydes, 2-formyl pyrroles, with the alkene component installed by *N*-substitution, were also suitable substrates. In the absence of the amine directing group, chiral phosphine ligands could promote the 7-membered ring formation in low (<30%) yields and ee's (<25%). In contrast, when using the chiral TDG, high yields and moderate enantioselectivities were achieved in the cyclisation (Scheme 2g).

2.2 C(sp^2)–H Functionalisation of Benzaldehydes

Aromatic aldehydes are desirable substrates for diversification by a wide variety of reactions, and so methods to access diverse benzaldehydes are of value. The weak coordinating properties of free aldehydes have previously been exploited for *ortho*-functionalisation of benzaldehydes with a variety of metals.[25] However, in the presence of more strongly coordinating groups the benzaldehyde directing ability is outcompeted.[26] A transient imine approach enables the reversible formation of a more powerful *N*-directing group, which can enable *ortho*-functionalisation in the presence of other potential directing groups.

In 2013 Seayad found that using a cationic rhodium catalyst in the presence of an aniline DG, benzaldehydes could dimerise to form phthalides (Scheme 3a).[27]



Scheme 3. Rh, Ir and Ru catalysed *ortho* C–H functionalisation of benzaldehydes using a transient imine directing group. Proposed metallacycles in grey boxes.

The electron poor aniline was proposed to condense with the aldehyde to form a TiDG, to promote formation of the *ortho*-rhodacycle. Association of a second aldehyde followed addition of the Rh–C across the carbonyl group instigates nucleophilic attack of the new Rh-alkoxide to the electrophilic imine carbon. β-Hydride elimination and hydrolysis steps then afforded the observed product. Aniline itself was a less reactive TDG and

electron rich anisidine ineffective. Electron rich, electron poor and *ortho*-substituted benzaldehydes were suitable substrates constructing the phthalides in >60% yield. When using a mixture of two aldehydes, with an unreactive (or less reactive) aldehyde to C–H functionalisation used in excess, heterocoupling could be facilitated in good yields and selectivity. Cheng used a benzylamine derived TiDG with benzaldehydes and nitrosobenzenes in an acridine synthesis (Scheme 3b).[28] A Rh^{III} catalyst promoted C–H amination through addition of a rhodacycle to the nitroso compound. Unusually, turnover of the benzylamine organocatalyst was proposed not to be through hydrolysis of the imine, but rather elimination of the amine on aromatisation of the product, following cyclisation by addition of the resulting aniline to the imine. Electron rich and some electron-poor substituents were demonstrated on the benzaldehyde and nitrosobenzene components, affording the product acridines in 41-88% yield

Using a similar rhodium and 4-trifluoromethylaniline catalysed system, Jiao showed very recently that dioxazolones could be used for *ortho*-amidation of benzaldehydes in high yields (Scheme 3b).[29] Following coordination of the metallacyclic intermediate to the dioxazolone, amidation is proposed via decarboxylation and migratory insertion steps.

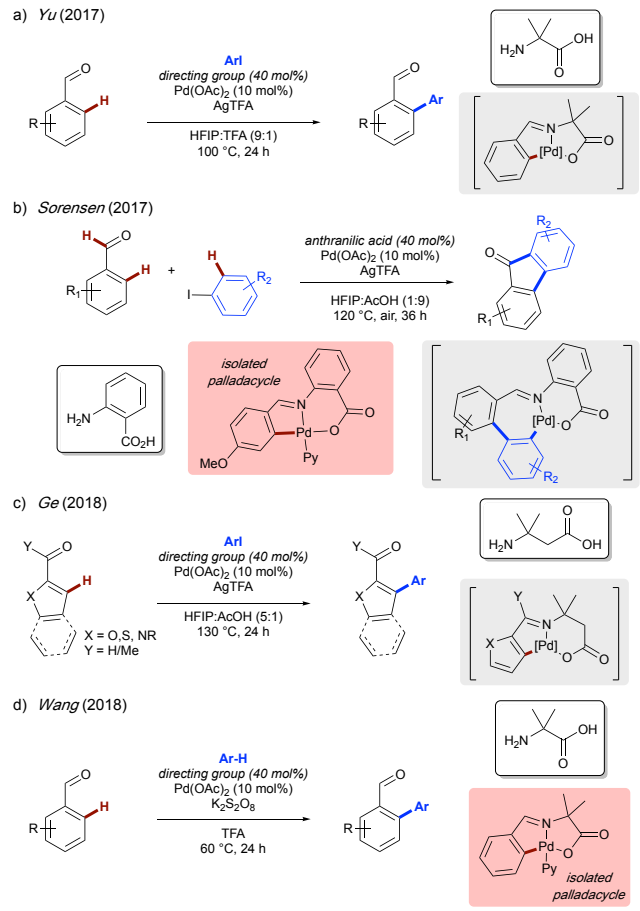
Yu, and Chen/He independently developed iridium catalysed *ortho*-amidation reactions with organic azides using electron poor anilines to form the TiDG (Scheme 3c,d).[30,31] Yu demonstrated good to excellent yields for the amidation of various aldehydes with *N*-tosyl azide, even in the presence of other strong directing functionalities. Chen and He included heterocyclic 2-thiophenecarboxaldehyde, which was amidated in 20% yield (compared to 98% with 2-fluorobenzaldehyde). In Chen and He's study, alternative sulfonyl azides were also investigated, which illustrated that both aromatic and aliphatic sulfonyl azides were effective. A single benzoyl-azide was also used under modified conditions to form a 4-nitrobenzamide in 65% yield. A related method was developed by Shi a year earlier, which required a discrete acid-mediated imine cleavage step to afford the product aldehyde.[32]

Zhang and co-workers recently developed a ruthenium catalysed *ortho*-alkylation of benzaldehydes with maleimides (Scheme 3e).[33] A monodentate TiDG formed from electron poor anilines, similar to those used in the ruthenium and iridium examples, was effective in promoting the reaction. Interestingly, the presence of the *ortho*-methyl group presented a larger effect on the reaction yield than the electronics of the aniline. The reaction scope was extensive and moderate to excellent yields (45–92%) were observed on highly functionalised benzaldehyde substrates containing sulfonamide, amide, ester, ketone and heterocyclic groups. Extensive diversification of the product was demonstrated forming various spirocyclic pyrrolidines. Zhang also showed that Ru was a suitable catalyst for *ortho*-C-H amination with organic azides, using electron poor anilines as the TDG (Scheme 3g).[34]

In 2017, Yu exemplified the use of palladium catalysis with TiDGs for the *ortho*-arylation of benzaldehydes. Bulky quaternary amino acid (2-aminoisobutyric acid) afforded the optimal bite angle to facilitate arylation (Scheme 4a).[30] The scope of benzaldehydes for the arylation reaction showed good tolerance of electron withdrawing and donating groups in the *ortho*, *meta* and *para* positions, to afford the arylated aldehydes in excellent yield. Importantly, *N*-tosyl-3-formylindole reacted to give the 4-arylated indole in 82% yield. For the aryl iodide scope, the reaction was tolerant of *ortho*-substitution (55% yield when using methyl 2-iodobenzoate). Unfunctionalised iodopyridines and iodothiophenes were unsuitable as coupling partners, however heteroarylation could be achieved on 2-substituted pyridines and thiophenes, where the coordination of the heteroatom to the catalyst is reduced. Iodoquinoline and iodoquinoxaline could also be used giving 33% and 40% yield respectively, with 15 mol% $Pd(OAc)_2$.

Sorensen used the TiDG approach in the synthesis of fluorenones with anthranilic acid as a catalytic TDG (Scheme 4b).[35] In this case, following palladium catalysed *ortho*-arylation of the benzaldehyde via the imine, a second $C(sp^2)$–H functionalisation occurred at the 2'-position of the resulting biaryl (see grey box, Scheme 4b). This intermediate underwent migratory insertion into the electrophilic imine carbon. β-Hydride elimination gave the product imine which hydrolysed to yield the fluorenone. A palladacycle derived from the imine was isolated displaying the acid as a second coordinating group. The isolated palladacycle was shown to form the fluorenone product under the reaction conditions. A series of substituted fluorenones were formed in one-pot in 14-63% yield by varying the benzaldehyde and aryl iodide. The method was also used to form the antiviral drug, Tilorone, in three steps.

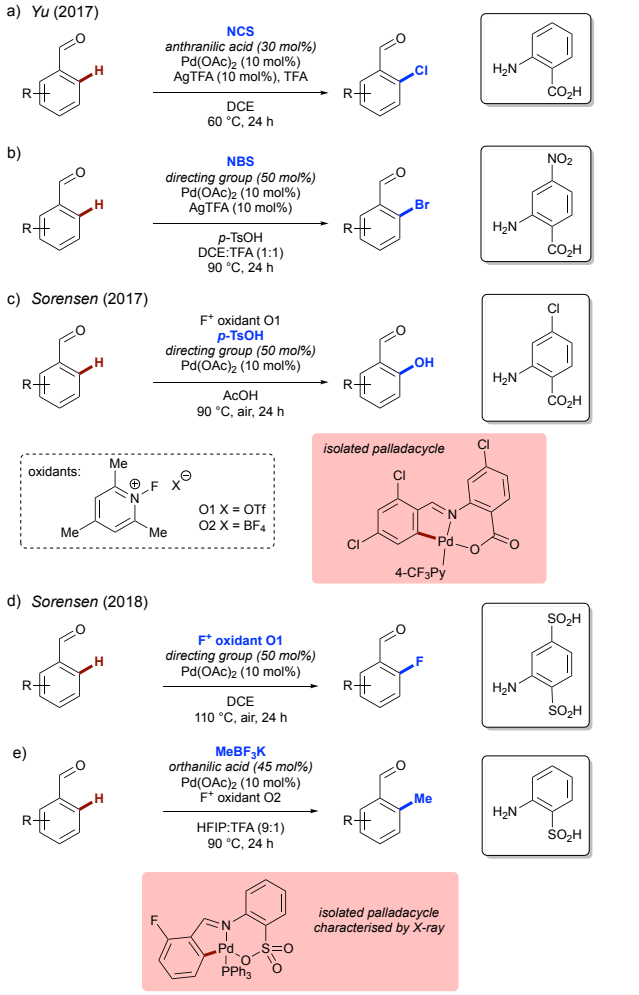
In 2018, Ge applied the TiDG methodology to the arylation of 2-formyl or 2-ketyl-5-membered heterocyclic systems using 3-amino-3-methylbutanoic acid as the TDG (Scheme 4c).[36] Thiophenes, furans, and *N*-protected pyrroles and indoles were arylated in good yields [for example 81% for benzothiophene-2-carbaldehyde and 51% for *N*-benzyl-pyrrole-2-carbaldehyde]. The optical properties of the 3-aryl thiophene products were explored for use as fluorescent dyes.



Scheme 4. C–H arylation of benzaldehydes. Proposed metallacycles in grey boxes. Isolated palladacycles in pink boxes.

Using potassium persulfate as an oxidant, Wang showed that a TiDG could facilitate dehydrogenative coupling of benzaldehydes with simple arenes such as benzene and anisole, used as solvent (Scheme 4d).[37] 2-Aminoisobutyric acid, as used by Yu in coupling with ArI, was shown to be optimal for the coupling, which occurred in good yields (52-75%). Mechanistically, following *ortho*-metallation of the imine to give a cyclometallated intermediate (a pyridine adduct of which was isolated) oxidation to Pd^{IV} by the persulfate was proposed. The second C–H activation of the simple arene occurred on this high-valent intermediate presumably by SEAr before reductive elimination afforded the arylated products. Excellent *para*-selectivity was achieved in coupling the arene partner.

In the same detailed study as the arylation (Scheme 4a), and amination work (Scheme 3c), Yu also demonstrated *ortho*-bromination and chlorination protocols.[30] Using 2-anthranilic acid and derivatives, with NCS or NBS, gave the *ortho*-halogenated products (Scheme 5a and 5b). The substrate scope and functional group tolerance for both of these reactions was excellent, forming the products in good to excellent yields in all cases. When the aldehyde substrate contained only a *para*-substituent, dihalogenation readily occurred. In the absence of the aniline directing groups, only trace products were formed. The halogenation and amidation reactions were used to functionalise complex substrates including an aldehyde derivative of Celecoxib, which was chlorinated in one-pot in 58% yield.



Scheme 5. Varied C–H functionalisation of benzaldehydes using anthranilic acid and orthanilic acid derivatives as TDGs. Isolated palladacycles in pink boxes.

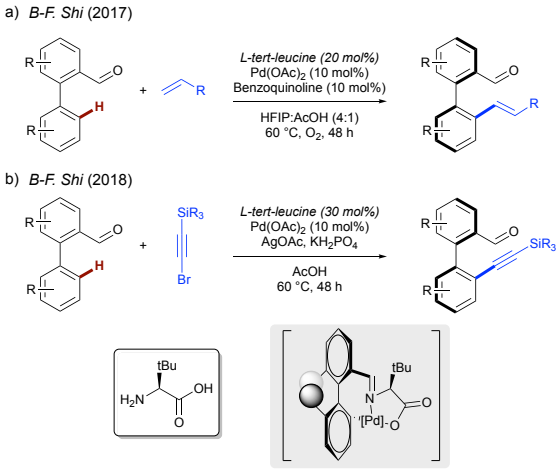
Sorensen showed that through when using a suitable external oxidant, *ortho*-hydroxylation of benzaldehydes could be achieved with toluene sulfonic acid as the hydroxyl source (Scheme 5c).[38] Chloro-anthranilic acid was used as the TDG, along with an F^+ source (O1) to oxidise the cyclometallated intermediate to a Pd^{IV}–F species. The fluoride ligand was displaced by TsOH to afford a suitable C–O reductive elimination substrate. Moderate to good yields (28–67%) were observed on a large variety of functionalised benzaldehydes. A pyridine stabilised palladacycle was isolated which formed the hydroxylated product in 18% yield when subjected to the reaction conditions. A chlorination reaction with the DCE solvent as the chloride source was also demonstrated. A hexafluoroisopropanol adduct could also be formed under modified conditions in a low yield.

Sorensen very recently reported orthanilic acids as TDGs for *ortho*-fluorination and methylation reactions of benzaldehydes, with a sulfonate as the secondary binding group (Schemes 5d and 5e).[39] With the TiDG formed from a bis-sulfonic acid derivative, reductive elimination of fluoride was achieved (Scheme 5d);

from a Pd^{IV}–F species similar to that proposed in the hydroxylation study (Scheme 5c). Optimisation of the fluorination conditions led to use of DCE as a solvent which enabled C–F bond formation in good yields (for example 3,4-dichlorobenzaldehyde, 69%), but also resulted in unwanted C–Cl reductive elimination. Again, electron rich and poor substituents on the benzaldehyde were well tolerated and heterocyclic 5-methylthiophene-2-carbaldehyde could also be fluorinated in 37% yield. For the methylation (Scheme 5e), a methyltrifluoroborate salt was used to introduce the methyl group to the cyclometalated Pd^{II}-intermediate through transmetalation. Orthanilic acid itself proved optimal as the TDG. In contrast, the corresponding carboxylic acid (anthranilic acid) resulted in a yield 40% lower. Both electron donating and withdrawing substituents on the benzaldehyde were well tolerated forming the methylated products in 37–73% yield. However, the reaction was limited to methylation, as β-hydrogens on longer alkyl chains of the trifluoroborate salt were not tolerated. A triphenylphosphine adduct of a palladacycle intermediate was isolated and structure confirmed by X-ray crystallography.

Shi has applied a chiral TiDG strategy to functionalise the 2'-position of biaryls with atroposelectivity.[40,41] Using chiral α-amino acid L-*tert*-leucine as the TDG, axially chiral biaryls were afforded by a Heck-type coupling with electron poor alkenes (Scheme 6a).[40] Depending on the bulk of the substrate, the reaction proceeded via dynamic kinetic resolution (DKR) or kinetic resolution (KR) pathways. Excellent *ee*'s of the olefinated products (95–>99%) were observed across the substrate scope. For the DKR, yields ranged between 40-98%; for the KR using conformationally stable racemic biaryls, the optically active olefinated products were formed in 30–47% yield with the starting materials recovered in 43–63% yield with 60–97% *ee*.

Shi later showed that L-*tert*-leucine was also a suitable TDG for the atroposelective C–H alkynylation of biaryls with bromoalkynes (Scheme 6b).[41] Here, the reaction was proposed to proceed via a Pd^{II}/Pd^{IV} redox pathway mediated by oxidative addition to the C–Br bond. High yields and enantioselectivities were observed across all biaryl substrates for both DKR (42-99% yield, 91–>99% *ee*) and KR (31–46% product yield, 93–99% *ee*) reactions. The highly functionalisable alkyne moiety was exploited for the development of new short syntheses of (+)-isoschizandrin and (+)-steganone with the C–H alkynylation as the key step.



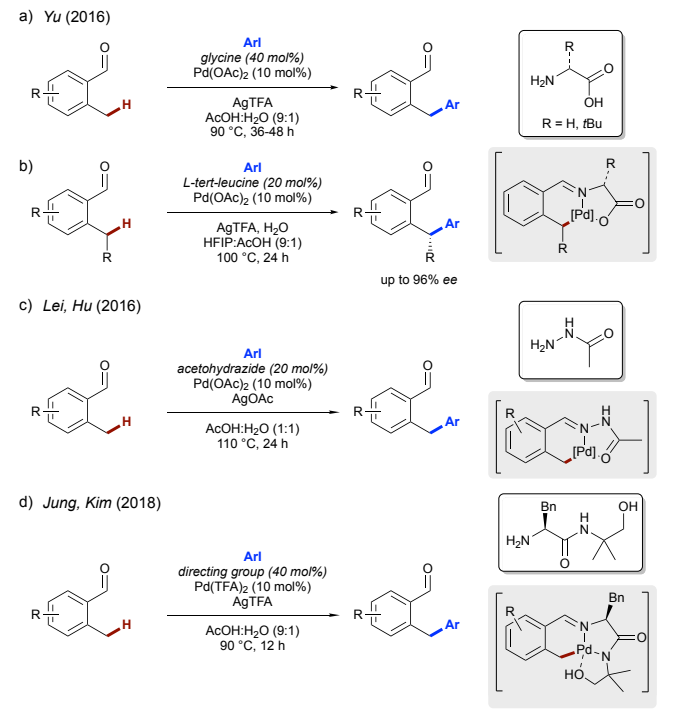
Scheme 6. Enantioselective synthesis of biaryls.

2.3 Benzylic C(sp^3)–H Functionalisation of Aldehydes

The first example using a transient imine directing group for the functionalisation of C(sp^3)–H bonds was by Yu in early 2016.[15] This seminal study presented three palladium-catalysed arylation protocols with aryl iodide coupling partners: racemic and enantioselective functionalisation at the benzylic centre of *o*-tolualdehydes and at the β-position of aliphatic ketones. All used readily accessible α-amino acids to form the TiDG. For the arylation of the benzylic position of *o*-tolualdehyde (Scheme 7a), 40 mol% of glycine and silver trifluoroacetate were used in AcOH as the solvent. Only trace amounts of products were seen when the reaction was conducted in DCE, toluene, dioxane or MeCN, which are more commonly used solvents for C(sp^3)–H arylation reactions with traditional amide DGs. Water was important in preventing decomposition of the imine.

Yields of 43–84% were achieved with aryl iodides bearing electron donating and electron withdrawing substituents as well as heteroaryl iodides such as 2-chloro-5-iodopyridine (57%). Sterically hindered examples gave lower yield (1-iodo-2-methylbenzene, 42%). Interestingly, free acids, hydroxyl groups and aldehydes on the aryl iodide could also be used. Methyl or halogen-substituents on the benzaldehyde gave similar yields.

An impressive enantioselective variant using *ortho*-alkylbenzaldehydes was also realised (Scheme 7b). L-*tert*-Leucine was found to be the optimal amino acid to form the chiral TiDG, with smaller side chains giving reduced enantioselectivity. In this case, using less of the directing group gave improved yields, assumed to be due to reduced saturation of the catalyst by the free amino acid. Using this approach 2-ethyl-5-(trifluoromethyl)-benzaldehyde could be coupled with methyl 3-iodobenzoate to afford the optically active C(sp^3)–H arylated product in 88% yield and 95% *ee*, for example. The origin of the stereoselectivity was assigned to steric interactions between the R group on the benzylic position of the substrate and bulky side chain of the amino acid.



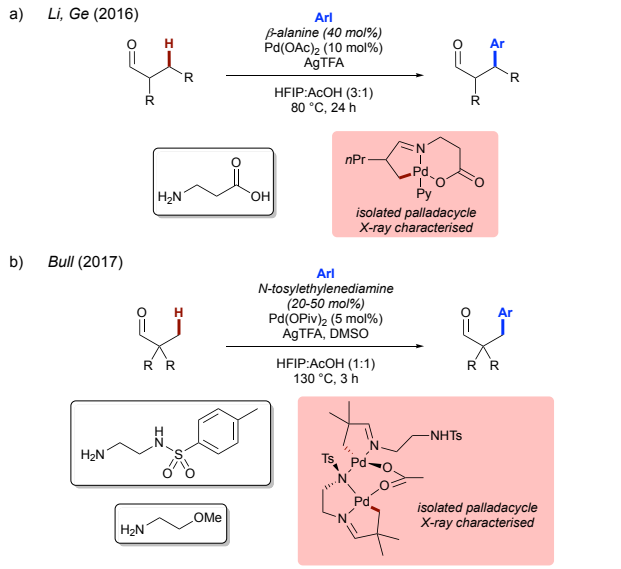
Scheme 7. Benzylic C–H arylation.

o-Tolualdehyde arylation was also achieved by Lei and Hu, this time using a transient hydrazone linkage (Scheme 7c).[42] Commercially available acetohydrazide was used to form the TiDG. As also seen by Yu, the reaction didn't progress in any solvents but acetic acid. They also found that the addition of water gave improved yields by assisting hydrolysis of the directing group from the arylated product. Electron rich and electron poor aryl iodides were installed in 42–93% yield but only trace product was observed when using *ortho*-substituted derivatives. 4-Iodopyridine was tolerated giving a 42% yield of the arylated product. Aryl bromides, tosylates and triflates were unreactive.

Very recently, Jung and Kim demonstrated that an amino amide bearing a pendant alcohol could form a TiDG for the benzylic arylation of *o*-tolualdehydes (Scheme 7d).[43] Unlike other directing groups used with palladium catalysis, the additional oxygen atom was proposed to be involved in tridentate binding of the metal. Furthermore, by changing the silver additive from AgTFA to AgOTf, adding an aniline additive and increasing the reaction temperature, cyclisation of the products occurred to afford anthracene derivatives in moderate yields.

2.4 C(sp^3)–H Functionalisation of Aliphatic Aldehydes

C–H Functionalisation at unactivated positions of aliphatic aldehydes was first explored by Li and Ge in 2016, using β-alanine as a TDG (Scheme 8a).[44] β-Methyl arylation of 2-methylpentanal was used as the model reaction when screening directing groups. Interestingly it was found that, although the α-amino acid, glycine, forms an effective TiDG for many substrates as described in this review, to achieve the activation of this secondary aldehyde a β-amino acid was required, due to the need for a 5,6- rather than 5,5-palladacycle. Arylation of β-methyl groups of simple aldehydes was achieved in 53–73% yield. When multiple reactive methyl groups were present in the case of isobutyraldehyde, a 1:1 mixture of mono and diarylated products was obtained. β-Methylene C–H bonds of secondary aldehydes could also be functionalised on both cyclic and β-branched substrates in lower yields [for example cyclopentane-carboxaldehyde 41% *cis*, 4.6:1 *dr*]. When using propanal as the substrate, some diarylated product from benzylic arylation was isolated in 8% yield, otherwise the reaction was chemoselective to unreacted methyl or methylene positions. There was no apparent trend in electronics of the aryl iodide when exploring the reaction scope, and even an *ortho*-trifluoromethyl aromatic was introduced in 61% yield. A palladacycle of a potential cyclometallated imine intermediate was prepared using pyridine as a stabilising ligand, and was characterized by X-ray crystallography. The palladacycle was an active substrate under the arylation conditions. Experiments using methylacrylaldehyde ruled out a possible oxidation/addition processes. The reaction did not occur in absence of the amino acid highlighting the need for imine formation.



Scheme 8. C–H arylation of aliphatic aldehydes.

We (Bull) demonstrated alternative directing groups for the β-arylation of tertiary aldehydes, with *N*-tosylethylenediamine proving most effective.[45] Using pivaldehyde, various ethylene diamine derivatives were investigated to determine how the secondary binding group might affect both the reactivity and the selectivity of the potential mono, di and triarylated products. Amides, sulfonamides abd ethers were all effective second coordinating groups, highlighting the potential for diverse and tunable TDG structures and the scope for further development of the field. The addition of DMSO as a stoichiometric additive led to improved yields. *N*-Tosylethylenediamine was most effective TDG (61% combined yield), though 2-methoxyethan-1-amine was also effective (56% yield) with a neutral second coordinating group (*cf* 55% for glycine). Oxygen-based secondary binding groups tended to result in a slightly higher tendency to form the multi-arylated products. Interestingly, monodentate TiDGs

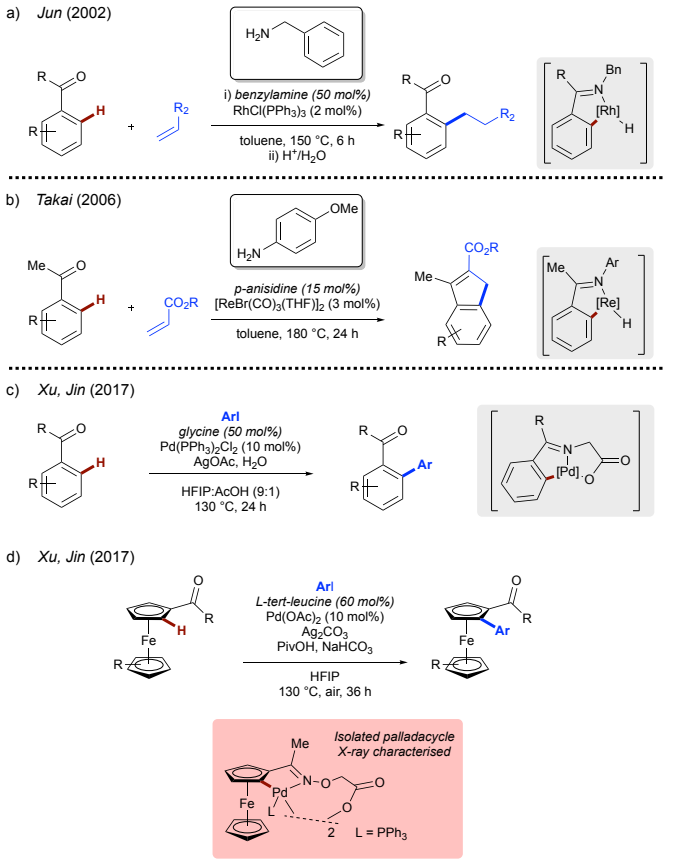
could also promote the arylation of pivaldehyde, but in lower yields; for example 17% for benzylamine. When no amine was present, no arylated product was observed. Varied electronics of the aryl iodide coupling partner were well tolerated, but *ortho*-substitution gave low yield. Tertiary aldehydes with one or two reactive methyl groups were arylated in moderate to good yields (32–55%). Similar results were obtained on larger scale with 20 mol% of the TDG. A palladacycle derived from the pivaldehyde imine with *N*-tosylethylenediamine was isolated and characterized by X-ray crystallography. The crystal structure revealed an unusual unsymmetrical dimeric species, which showed both monodentate (imine) and bidentate (imine and sulfonamide-N) binding modes of the TiDG, as well as a bridging acetate ligand. The dimer was active catalyst in the arylation. When dissolved in AcOD-d_4 the dimer formed a monomeric species, characterised in solution, likely to be in equilibrium between chelation of the imine directing group and the acetate ligand. These results were suggestive of a hemi-labile role for the second coordinating site of the TiDG.

3. C–H Functionalisation of Ketones

Ketones present additional challenges compared to aldehydes due to reduced rate of imine formation and hydrolysis and the greater possibility of forming *E* or *Z* imines, with potentially inactive geometries. To date, the use of TiDGs for ketone substrates has been less well explored with only five fully 'transient' examples across sp^2 and sp^3 C–H bond functionalisation reactions.

In 2002 Jun *et. al.* found that benzylamine could be used to furnish an imine directing group *in situ* for the *ortho*-alkylation of aromatic ketones using a rhodium catalyst (Scheme 9a).[46] Due to the higher stability of the ketimine (*cf* aldimine), the total yield of the ketone product was only revealed after hydrolysis of the residual ketimine. Related to this study is Jun's ketimine alkylation, where difunctionalisation of benzaldehyde using a TiDG via a ketone intermediate was also exemplified.[47] Takai found that a TiDG formed from an electron rich aniline gave the highest yields for a rhenium catalysed annulation of aromatic ketones with activated alkenes (Scheme 9b).[48] This is in contrast to the reaction with aldehydes, where electron poor anilines were preferred. The reaction was sensitive to both electron poor and sterically demanding groups on the aldehydes, which both gave much reduced yields. For example, *o*-tolylmethylketone and 4-triflourophenylmethylketone with ethyl acrylate gave 11% and 37% isolated yields respectively, whereas phenyl methyl ketone with the same alkene gave a 93% yield.

Xu and Jin showed that palladium catalysed *ortho*-arylation of aromatic ketones was feasible when using glycine to form a TiDG (Scheme 9c).[49] Various electron rich, poor and sterically demanding aryl iodides were installed in good yields (27–90%, with enhanced yield for some examples when using $Pd(OAc)_2$ as the catalyst. Moderate to good yields were observed across all substituted aryl ketone examples (49–88% yield). Consistent with previous findings (see scheme 7), the benzylic C(sp^3)–H of the *ortho*-methyl group on *o*-tolylmethylketone was arylated in preference of the *ortho*-C(sp^2)–H. Kinetic isotope effect studies suggested that the C–H metallation step was likely to be rate determining and irreversible.

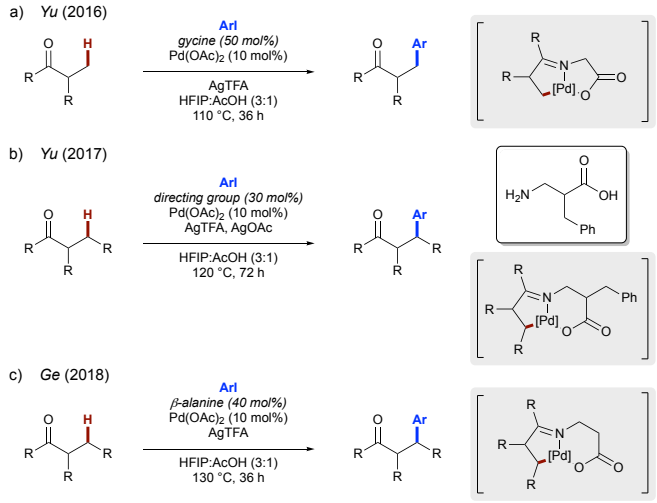


Scheme 9. C–H arylation of aryl ketones.

The same group applied this approach to the enantioselective arylation of ferrocenyl ketones using L-*tert*-leucine to form a chiral TiDG (Scheme 9d).[50] All examples exhibited *ee* >93%. In general, electron poor aryl iodides exhibited higher reactivity, with electron rich and neutral examples being formed in lower yields [3-nitroiodobenzene, 75%; 4-iodoanisole, 38%]. Interestingly when using a ferrocene with a formyl group on the second cyclopentadiene ring, only the ring containing the ketone group was functionalised. Although the L-*tert*-leucine palladacycle could not be isolated, a palladacycle of a related oxime system was successfully formed and characterised once stabilised with a triphenylphosphine ligand. The methodology was applied to the synthesis of a novel ferrocenyl-phosphine ligand, which was shown to afford moderate enantioselectivities for a palladium catalysed annulation reaction.

Yu's 2016 paper reported the β-arylation of unactivated aliphatic ketones with glycine as a TDG (Scheme 10a).[15] The conditions optimised for *o*-tolualdehydes (Scheme 7a) produced only trace amounts of the ketone product even at elevated temperatures. However, improved yields were obtained when removing the additional water. Amino acids with bulky side chains led to reduced reactivity, likely due to less favourable imine formation. Yields of 47–71% were obtained of the monoarylation product with electron rich and electron poor *para*- and *meta*-substituted aryl iodides, but *ortho*-substitution or

heterocycles were not demonstrated. For ketones containing multiple reactive methyl groups, diarylation readily occurred. Methylene C–H activation was possible on cyclopropyl, cyclobutyl and cyclohexyl rings, with a *cis*-stereochemistry proposed for all rings based on NOE analysis. γ-Arylation occurred in good yields on a single substrate bearing no β-C–H bonds (49% mono, 12% di). Aliphatic aldehydes were not tolerated under these conditions.



Scheme 10. C–H arylation of aliphatic ketones.

Yu later published improved conditions for methylene arylation of acyclic ketones (Scheme 9b).[51] A β-amino acid was used, functionalised with a benzyl group (β-to the amine), which showed enhanced reactivity compared to β-alanine (71% and 57% respectively). Substitution at the α-position of the amine in the TDG resulted in reduced yields due to less favourable imine formation. A methyl ester and amide derivative of β-alanine resulted in very low yields. A mixture of silver salts were used, to suppress the formation of a homocoupled Ar-Ar by-product. This gave a 15% improvement in yield from AgTFA alone. The reaction proceeded in good yields (33–83%) with electron poor and electron rich aryl iodides, and *ortho*-substituents would also be incorporated in lower yields [for example 1-iodo-2-methylbenzene, 33% yield]. Various functionalities including ethers, esters and a phthalamide protected amine were tolerated on the ketone substrates (39–71% yield). Ketones with a branch at the α-position gave complex mixtures of products with low yields. Recently, Ge also showed that β-alanine was a suitable directing group for β-methylene ketone arylation (Scheme 10c).[52]

4. C–H Functionalisation of Amines

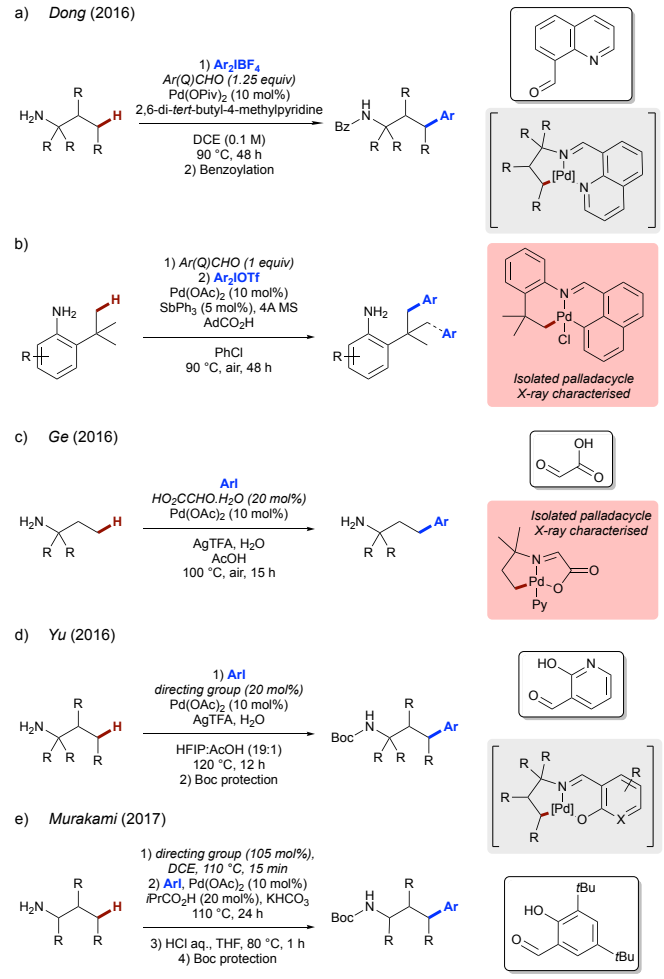
Transition metal catalysed functionalisation of amines is a significant challenge due to the high binding affinities of free amines to metal centres.[53] For palladium, this leads to the formation of stable bis-amine Pd complexes.[54] α-Oxidation can also occur to form unwanted imines in a competing pathway.[55] To date there are very few examples of amine functionalisation using a TiDG, published in quick succession in 2016. All are covered here, though not all are fully transient, requiring stoichiometric directing groups, or work up steps.

Dong released the first direct arylation of free amines using quinoline-8-carbaldehyde to form the imine DG (Scheme 10a).[56] The reaction was γ-selective due to the more facile formation of the 5-membered over 4-membered palladacycle. All of the products were derivatized by benzoylation to aid isolation and due to volatility of some of the products. Diaryliodonium salts were required as the coupling partner, with the BF_4^- counterion giving the best results. The reaction was optimised on 2-aminobutane, and in the absence of a directing group no arylation occurred. Using bulky 2,6-di-*tert*-butyl-4-methylpyridine was optimal to neutralise the HBF_4 generated, although insoluble inorganic bases such as $Ba(OH)_2$ also gave moderate yields. Electron poor aromatics were installed in the best yields. Iodobenzene gave 70% yield, but 4-iodoanisole gave 37% yield despite an elevated temperature and longer reaction time. An *ortho*-fluoro substituent was well tolerated (63%) but no heteroaromatic examples were given. Amines with two hydrogens on the α-carbon were tolerated in lower yields. In many cases, diarylation on the new benzylic position occurred, most significantly on *tert*-amylamine (40% yield, mono:di 1.2:1). Three examples of methylene C–H activation on linear or cyclic substrates were given in 41–77% yield. On a large scale, it was shown that the quinoline aldehyde could be recovered in 78% yield. Catalytic use of the TDG was also demonstrated in reduced yields.

In the same study, C(sp^3)–H arylation of 2-*tert*-butylaniline derivatives was also demonstrated (Scheme 11b).[56] The imine could be formed *in-situ* but improved yields were seen when premixing the aniline and aldehyde for 1 h. The addition of catalytic $SbPh_3$ gave slightly improved yields and higher consistency of results. Interestingly the reaction was completely shut down on omission of the adamantane carboxylic acid or the molecular sieves, but saturation of the sieves with 100 μL water didn't cause a significant drop in yield. Electron poor diaryliodonium salts and electron rich anilines were most reactive [the *para*-trifluoromethyl diaryliodonium salt formed the mono and diarylated products in 48% total yield, 39% for the phenyl]. A chloride derivative of a potential intermediate palladacycle was isolated from the pre-formed imine, which was characterised by X-ray crystallography.

Ge showed that aryl iodides could be used as the coupling partner for aliphatic primary amines with glyoxylic acid as a TDG (Scheme 11c).[57] Interestingly, the reaction worked in 10% yield in the absence of any ligand, meaning that the primary amine can act as a monodentate directing group itself. Alternative TDGs were investigated, but all other aldehydes (including Dong's formyl quinoline) gave yields lower than the reaction in absence of ligand. All *meta*-, *para* and di-substituted aromatics or heteroaromatics investigated were installed in 42–73% yield, though *ortho*-substituted examples were unreactive. All amines needed a fully substituted α-carbon for reactivity. Methylene C–H arylation was observed on a cyclic substrate (2-cyclohexylpropan-2-amine, 23% yield, *cis*). The products were purified by acid/base workup without the need for chromatography. The arylation was used to make a series of

Fingolimod analogues. A pyridine derivative of a potential palladacycle was isolated and characterised by X-ray crystallography. The palladacycle was also an active substrate undergoing arylation in 72% yield with no additional catalyst or directing group. The catalytic cycle was proposed to proceed via a Pd^{II}/Pd^{IV} redox cycle.



Scheme 11. C–H arylation of primary unprotected amines using imine directing groups.

Yu developed a highly active TiDG for the γ-arylation of amines using commercially available 2-hydroxynicotinaldehyde (Scheme 11d).[58] The products were derivatised by Boc-protection to aid purification. Only acidic solvents were suitable, and the best yields were achieved with HFIP as a co-solvent. The reaction did not work in absence of a directing group or without the crucial imine forming carbonyl component. Similarly, when the aldehyde was moved to the 4-position of the pyridine, only trace product was formed. Good yields were observed for even sterically demanding aryl iodides [61% for 2-bromoiodobenzene] and both electron rich and electron poor aryl iodides were suitable [80% for 4-methoxy and 83% for 4-nitro substituted aryl groups]. On the reactive γ-methyl of 2-methylbutan-1-amine, *N*-heteroaryl iodides were demonstrated to form functionalised amines in 40–76% yield. The reaction was also successful for the arylation of methyl groups of wide variety of amine structures, including unbranched propan-1-amine which was arylated in a remarkable 68% yield. For *tert*-amylamine, which has *geminal*-methyl groups on the α-carbon, significant diarylation occurred at the benzylic position of the monoarylated product (61%, mono:di 1:2.8). To achieve functionalisation on methylene groups, more forcing conditions were necessary and the yields were decreased [for example octan-1-amine was arylated in a 43% yield at a temperature of 150 °C]. Generally, cyclic or branched substrates gave higher yields for the methylene arylation. The reaction was performed on a large scale with significantly lower loadings of catalyst and directing group (2 mol% and 4 mol% respectively) resulting in a 61% isolated yield of the arylated cyclohexanamine.

Finally, Murakami showed that bulky salicaldehydes could present a removable and recoverable directing group for the γ-arylation of primary amines through a stepwise but telescoped protocol (Scheme 10e).[59] *tert*-Butyl groups on the TDG were important to prevent bis-imine-Pd complexes. The reaction was selective for methyl positions and 72% yield was obtained with *sec*-butyl-amine using 4-iodotoluene. Methylene positions could also be functionalised on bicyclic *exo*-2-aminonorbornane and benzylic 2-ethylaniline in 55% and 87% yields respectively. The reaction scope was demonstrated using with stoichiometric amounts of the DG, but it could be used at 20 mol% for benzylic arylation of 2-ethylaniline with only a slightly diminished yield (69% at catalytic vs 78% stoichiometric).

Conclusions

Transient imine directing groups provide an attractive alternative to traditional directing groups for the functionalisation of both C(sp^2)–H and C(sp^3)–H bonds. As has been demonstrated in this review, TiDGs are capable of being formed, mediating C–H functionalisation and being cleaved all in one reaction pot. This provides single operation functionalisation protocols from simple starting materials using only common and useful existing functionality in the substrate. These 'next generation' DGs have already been successfully used with a range of metal catalysts to form C–C and C–X bonds. In many cases, metallacycles have been formed to support the imine intermediates, and mechanistic studies support the transient imine hypothesis. This review has focused on C–H functionalisation of transient imines, covering work published up to the end March 2018.[60,61] However, this remains a fledgling field. There are many opportunities to improve and exploit other substrates and bond formations.

Considerable progress has been made on functionalisation of aromatic aldehydes with a variety of metal catalysts, however there are few examples on aliphatic ketones, and as yet the C(sp^2)–H functionalisation of aromatic amines has not been achieved. For more challenging aliphatic substrates, the TiDG approach thus far, has been limited, to that of palladium-catalysed arylation. This is likely to be due to the reaction conditions required for reversible formation of the imine, which may cause problems in compatibility with other functionalisation strategies. However, using inspiration from the progress made on aromatic substrates and using other metals, this will likely be addressed in the near future. Furthermore, to date only few

designs of TDGs have been examined, which have dramatic effects on the success of proposed reaction.

We expect future developments in this field which will extend the utility and potential application of C–H functionalisation strategies, facilitating functional group tolerant and late stage functionalisation reactions.

Conflicts of interest

There are no conflicts to declare.

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