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When is an Imine Directing Group a *Transient* Imine Directing Group in C–H Functionalization?

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'Transient' C–H functionalization has emerged in recent years to describe the use of a dynamic linkage, often an imine, to direct cyclometallation and subsequent functionalization. As the field continues to grow in popularity, we consider the features that make an imine directing group transient. A transient imine should be i) formed dynamically *in situ*, ii) avoid discrete introduction or cleavage steps, and iii) offer the potential for catalysis in both the directing group and metal. This concept article contrasts transient imines with pioneering early studies of imines as directing groups for the formation of metallacycles and the use of preformed imines in C–H functionalization. Leading developments in the use of catalytic additives to form transient directing groups (as aldehyde or amine) are covered including selected highlights of the most recent examples of catalytic imine directed C–H functionalization with transition metals.

1. Introduction

Substrates for catalytic C–H functionalization typically rely on a directing group to position a transition metal catalyst. From pioneering investigations into fundamental cyclometallation chemistry that underpins much of modern C–H functionalization,[1] to the current state of the art in this field,[2] imine directing groups continue to prove themselves to be powerful directing groups to achieve C–H activation.[3] Imines are readily formed by the condensation of aldehydes/ketones with amines. The Lewis basic imine nitrogen is capable of coordinating to a variety of metals and its lone pair is well positioned to bind in a suitable orientation to promote cyclometallation. A second binding element can be readily introduced (e.g. CO_2H, CONHR, phenolic OH) to create an appropriate binding pocket to promote C–H activation of a particular centre. The high tunability of these directing groups makes them highly versatile for functionalizing both carbonyl and amine substrates (Figure 1).

The earliest example of directed C–H functionalization was reported by Murahashi in 1955, which used an imine directing group to achieve carbonylation of aldimines (Scheme 1A).[4] It was not until sometime later that studies of fundamental cyclometallation chemistry were conducted, many of which used imine and oxime directing groups.[5] Early investigation in the C–H activation of pinacolone oxime by Shaw led to the isolation of a dimeric palladacycle (Scheme 1B). A later study by Dyke using *N*-benzyl imines, isolated similar dimeric palladacycles.[5a] These key early studies exemplified imines and oximes as directing groups for cyclometallation, although they did not explore subsequent derivatization. Later work by Sames explored the use of imines in stoichiometric C–H activation for key synthetic steps in the synthesis of antibiotic Rhanzinilam[7] and the core of Teleocidin B4.[8]

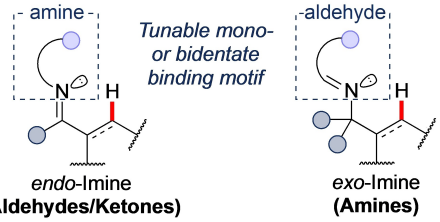

Figure 1. Versatile imine directing groups.

Building on these fundamental studies, the use of imines and oximes as directing groups for C–H functionalization has increased dramatically. Sanford demonstrated the use of oximes (and imines to a lesser extent) for C(sp^2)-H and C(sp^3)-H functionalization (Scheme 1C).[9] More recently, C(sp^2)-H alkenylation, metal-free C(sp^2)-H borylation and arylation were developed with stoichiometric imine.[10] In addition to aldehyde/ketone functionalization, the use of stoichiometric imine directing groups have also been applied to amine functionalization, such as in the work of Dong who used 8-formylquinoline as a stoichiometric additive to form the iminoquinoline directing group *in situ*.[11] Imines have also found success in templated approaches for remote C–H functionalization of amines and aldehydes as demonstrated by the notable work of Maiti for distal arene functionalization.[12]

Recent efforts have focused on the use of imines as 'transient' directing groups. By capitalizing on the uniquely labile imine linker, it is possible to achieve *in situ* directing group installation and removal steps without the need to isolate the intermediate imine. This was first demonstrated by Jun,[13] for the rhodium catalysed C–H alkylation of aldehydic C–H bonds to generate ketones (Scheme 2). These methods

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used a catalytic amine additive (amino pyridine or amino acids respectively) to form the directing imine *in situ* to bind the metal and effect C–H functionalization. In the work described by Yu, the use of HFIP as the solvent was crucial to promote the reaction and has found widespread use in transient C–H functionalization due to its unique solvent properties.[15]

The popularity of this approach using imines has resulted in transient imines becoming increasingly synonymous with transient directing groups, despite these concepts being distinct.[16] This article aims to define what makes a directing group 'transient' and evaluate why catalysis in the transient directing group can be achieved. Selected significant developments in the field since 2022 are highlighted that use a competent catalytic transient directing group with no preformation of imine, and no additional hydrolysis steps. Important conditions to achieve catalysis are highlighted. This concept article cannot be comprehensive and focuses on selected recent examples of new transformation and advances in conditions in which a low loading of TDG is employed ($\leq$30 mol%) and goes beyond previous reviews. Examples are subdivided into aldehyde, ketone, and amine functionalization reactions where the linking functionality remains intact and immediately available for further derivatizations.

2. What Defines a Transient Directing Group?

The term 'transient directing group' is often used interchangeably to refer to either the aldehyde/amine additive or the resultant imine formed as a result of condensation between the additive and the functionality on the substrate. Since the imine is acting as the directing group which is exemplified in the conceptual catalytic cycle described in scheme 3, it is most accurate to describe the *in situ* formed imine as the transient directing group and will be referred to as such in this article. For a directing group to be defined as 'transient' the following criteria should be met:

- **Dynamic DG formation/cleavage:**

The major factor defining a transient directing group is that it is formed and cleaved in a highly dynamic and reversible manner. This results in the transient directing group existing only temporarily and is hence a transient species in the reaction.

- **No discrete DG installation or removal steps:**

A knock-on effect of the highly dynamic nature of the TDG results in it being 'removed' as part of the reaction. No additional steps for directing group formation or hydrolysis should be required.

- **Potential for catalysis:**

Finally, a consequence of the dynamic nature of the TDG is that it can be regenerated in the reaction, allowing the additive to be used catalytically. This is particularly important for enantioselective C–H functionalization, using sub stoichiometric chiral additives.

An additional complication presents itself in the form of rate matching, in which the lifetime of the TDG needs to be just long enough for C–H functionalization to occur, but short enough to be hydrolysed to allow the two catalytic cycles to work cooperatively. Thus, a variety of tactics have been employed to achieve the right rate of TDG formation and C–H functionalization. Often this is achieved by directly controlling the imine equilibrium by the use of additives or HFIP as solvent. Commonly, the TDG precursor additive itself possesses an acidic second binding site which can aid in achieving reversible imine formation/cleavage. Alternatively, bespoke ligand additives

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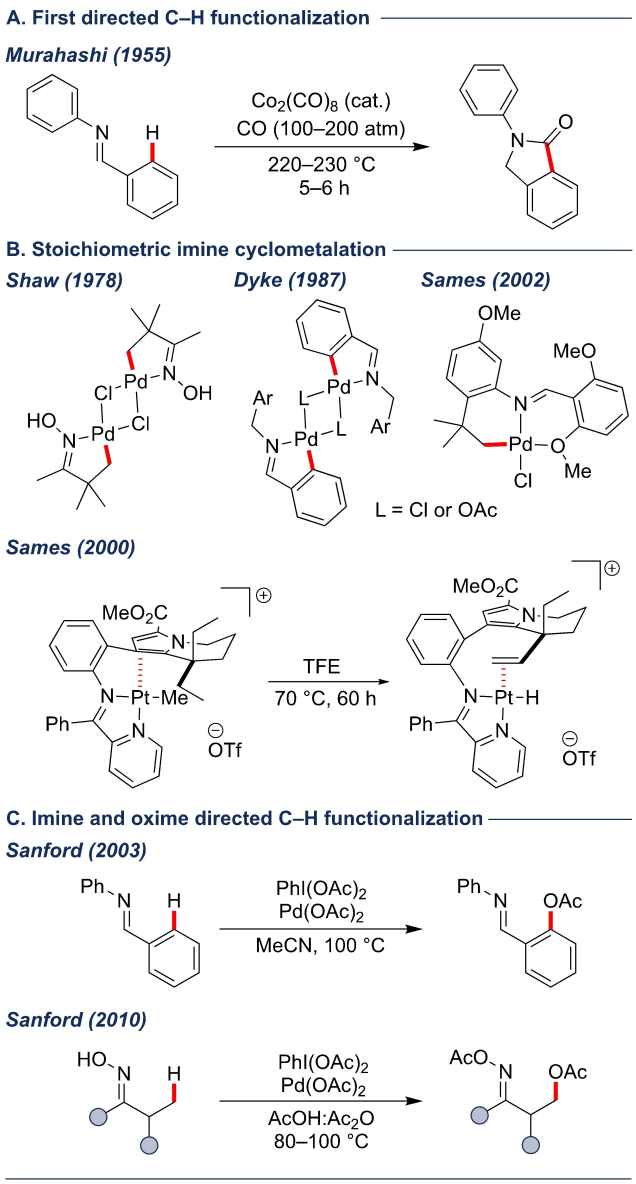
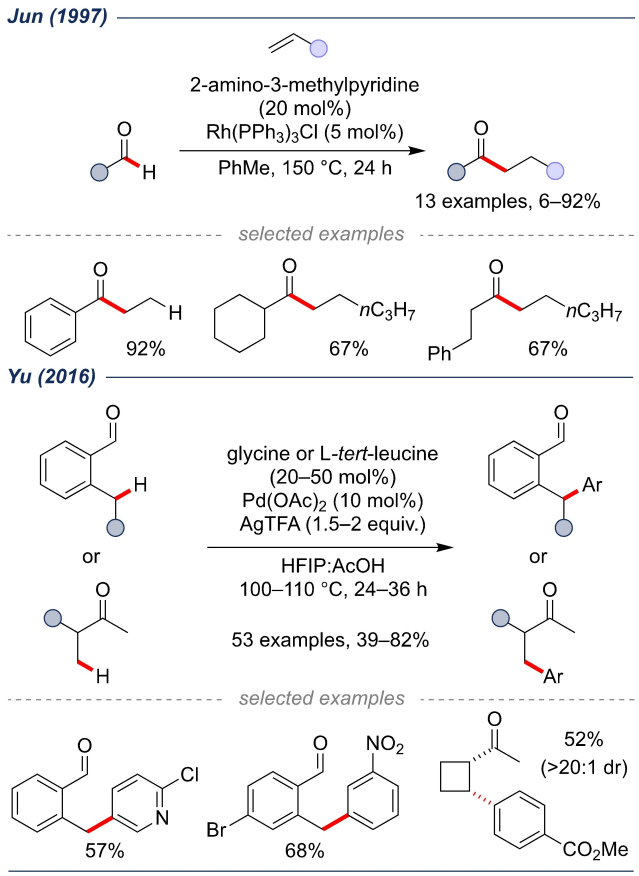
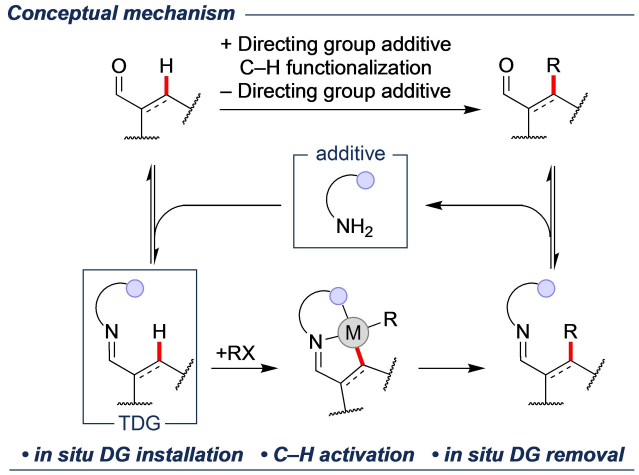


Scheme 1. A) First example of directed C–H functionalization B) Notable isolated imine and oxime metallacycles formed by C–H activation. C) Recent example of oxime and imine directed C–H functionalization.



Scheme 2. Seminal works of transient C–H functionalization.



Scheme 3. Conceptual transient imine directing group, exemplified with an aldehyde linked TDG.

have been developed to increase the rate of C–H functionalization and thus improve rate matching.

3. Aldehyde and Ketone Functionalization

Aldehydes are highly electrophilic with a diverse reactivity profile, making them widely used building blocks in organic synthesis. Aldimines form and cleave readily in a highly dynamic process, and aldehyde functionalization remains one of the most popular avenues of transient C–H functionalization. In the case of alkyl aldehydes, the higher electrophilicity of the aldehyde generally makes the transient imine directing group less stable and readily cleaved leading to a more readily reversible process. Generally, this results in a finer requirement in the timings of the key steps (imine formation and C–H functionalization).

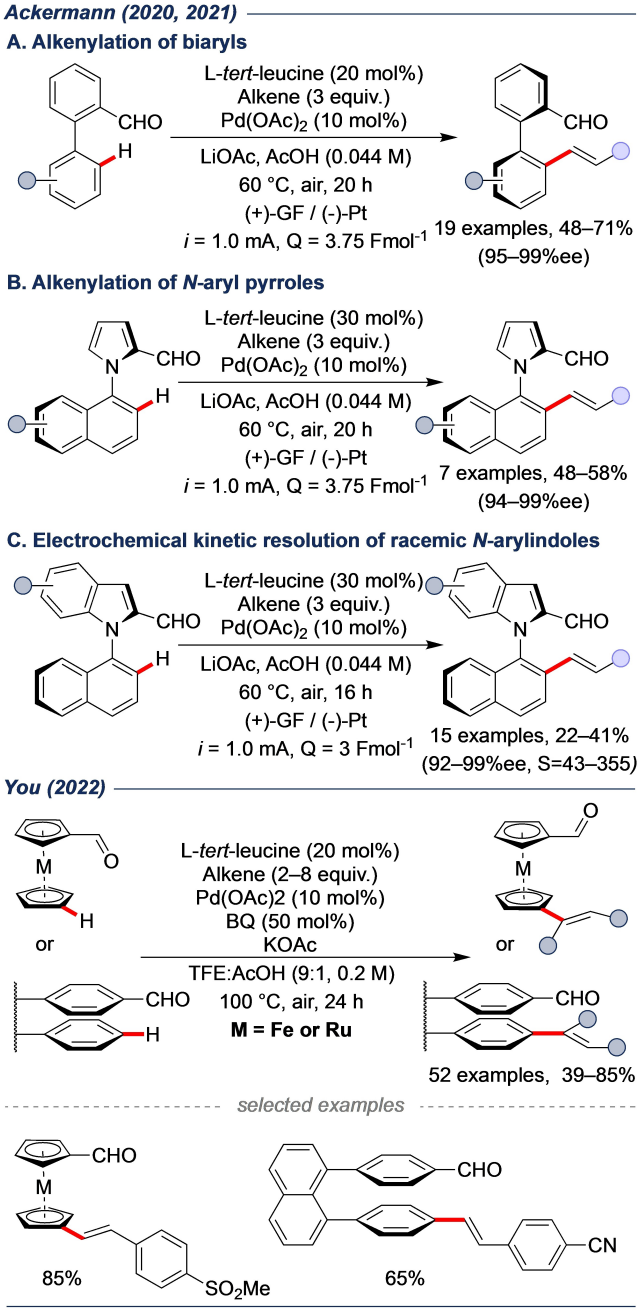
Since Yu's seminal report in 2016,[14] several leading reports have been published achieving the C–H functionalization of aldehydes. Yu and Sorensen have reported powerful transient C(sp^2)-H functionalization methodologies for the arylation, amidation, halogenation,[17] hydroxylation,[18] fluorination, and

methylation[19] of benzaldehydes. The development of C(sp^3)-H functionalization remains more focused on arylation,[20] though some investigation into C–F, and C–O bond forming methodologies have been reported.[21] These earlier reports tended to use high TDG loading (approaching 50 mol%) with yields only slightly higher than the loading, implying the TDG to be a poor catalyst. Recent investigations have developed reaction conditions to improve the catalytic competency of the transient directing group.

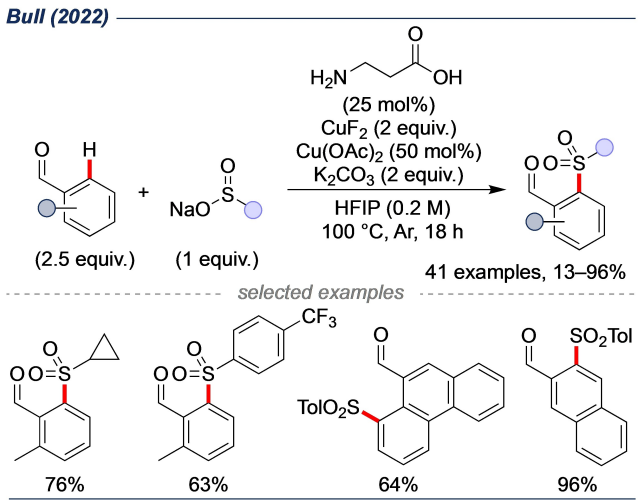
The use of transient imine directing groups for C–H functionalizations via Pd^{II}/Pd^0 mechanistic cycle have also been developed (Scheme 4).[22–24] Ackermann reported an atroposelective, pallada-electrocatalyzed C–H alkenylation method to functionalize biaryls and *N*-aryl pyrroles with L-*tert*-leucine (20–30 mol%) as the amine additive to form the TDG. The process was further developed to enable atroposelective electrochemical kinetic resolution of racemic *N*-arylindoles with selectivity factors (*S*) up to 355.[23] On the other hand, You demonstrated the palladium interannular C(sp^2)-H alkenylation of metallocenes and stacked aromatic systems.[24] L-*tert*-Leucine (20 mol%) was used to form the TDG, with a TFE:AcOH mixed solvent system to aid turnover of the catalytic amino acid. The unique selectivity for a more distal aromatic system was proposed to result from alkene coordination promoting migration of palladium and resulting in the functionalization of the more distal aromatic ring. A fluorinated and acidic solvent system was key to ensuring highly dynamic TDG formation and facilitate dissolution of O_2. More recently, Rezayee reported an atroposelective bromination to access chiral biaryl scaffolds *via* the transient imine directing group strategy.[25]

Few examples of metals other than Pd in transient C–H functionalization have been reported, with limited examples using rhodium, ruthenium, iridium and cobalt.[26] There are notably few examples using base metals. In 2022, we (Higham and Bull) reported using copper salts with β-alanine as a catalytic additive (25 mol%) to form a TDG to achieve C(sp^2)-H sulfonylation of benzaldehydes (Scheme 5).[27] The copper salts used may also promote reversible imine formation/cleavage by acting as a Lewis acid. This enabled the synthesis of a variety of sulfones though an oxidative coupling of sulfinate salts and benzaldehydes. Product inhibition effects were observed which were attributed to a relatively stable copper ligated product imine forming and trapping the amino acid additive. The use of the aldehyde in excess alleviates product inhibition by shifting the reaction equilibrium to forming more starting material imine to promote the desired reaction.

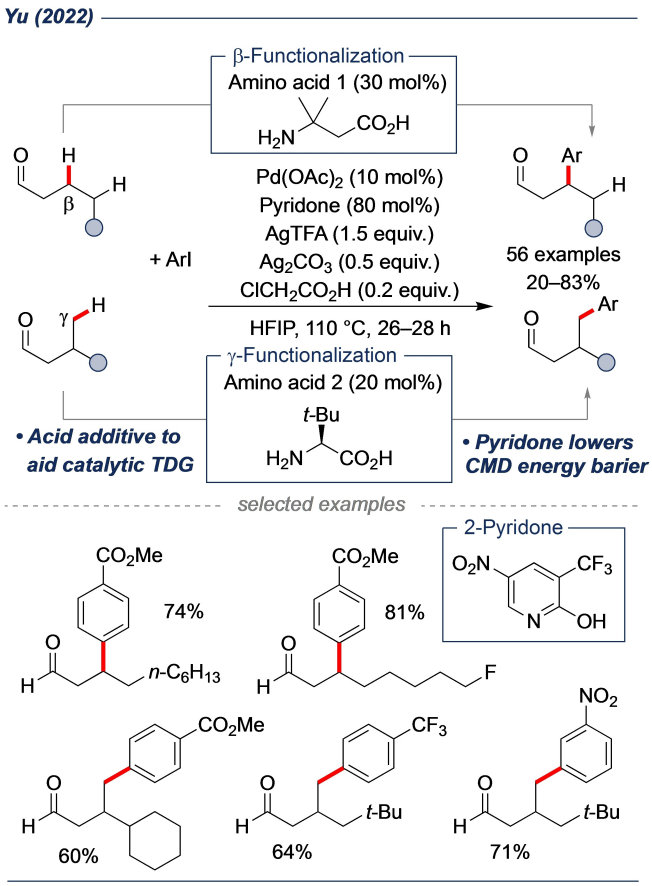
Yu disclosed the arylation of primary alkyl aldehydes at β- and γ- positions using an amino acid additive and an additional pyridone ligand (Scheme 6).[28] Regioselectivity was determined by the specific binding mode of the transient directing group,



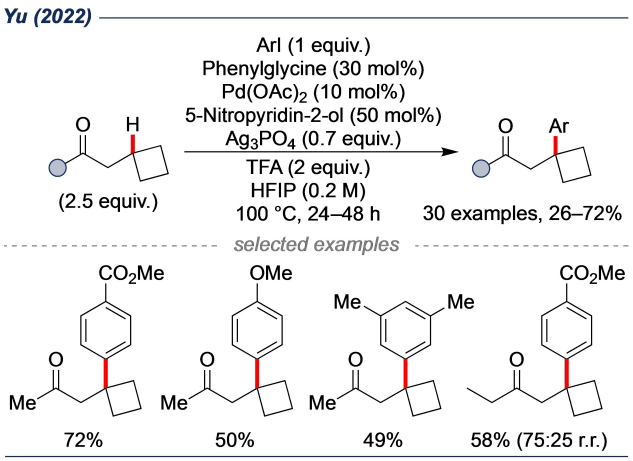
Scheme 4. C–H alkenylation of aldehydes with transient directing group.



Scheme 5. Copper mediated transient C–H sulfonylation.



Scheme 6. Site-selective β- and γ-C–H arylation of aldehydes.



Scheme 7. Selective tertiary C–H arylation of cyclobutylmethyl ketones.

in which β-functionalization was favoured when a [5,6]-chelation mode with amino acid 1, and γ-functionalization is favoured by a [6,5] chelation mode with L-*tert*-leucine. In both cases, a relatively low amino acid catalyst loading was used. Pyridone ligand additives have been employed in transient C–H functionalization and are proposed to be a surrogate for a carboxylate,[29] lowering the energy barrier of the CMD step and in this case allowing the C–H activation to occur, with no reaction observed in its absence. The use of chloroacetic acid was proposed to aid in the reversibility of imine formation to lower the effective loading of the amine additive, to below that of another powerful method reported contemporaneously by Maiti and Ge for the β-arylation of primary aldehydes.[30]

There has been less extensive development of ketones in transient C–H functionalization. In comparison to aldehydes, ketones are less electrophilic, can readily tautomerize if there are α-C–H bonds present, and present different steric requirements for the transient directing imine to achieve a reactive conformer.

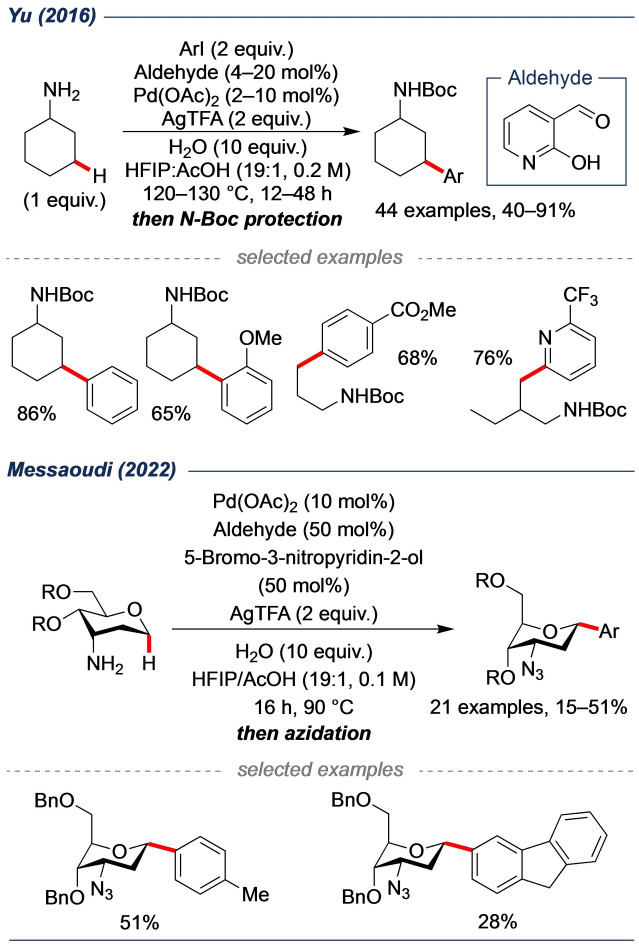
A fascinating report by Yu in 2022 disclosed the first transient C–H functionalization strategy to be selective for tertiary C–H bonds (Scheme 7).[31] The functionalization of tertiary C–H bonds has been extremely challenging using Pd catalyzed methods. Importantly the strained geometry of the cyclobutane unit increased the s character in the C–H bonding orbital, further facilitating C–H activation. Use of the ketone substrate in excess also promoted the reaction, and a pyridone additive was required to enable the reaction. To promote turnover of the transient directing group, HFIP is used as the solvent in the reaction, with trifluoroacetic acid as an additive to ensure a reversible imine formation.

4. Amine Functionalization

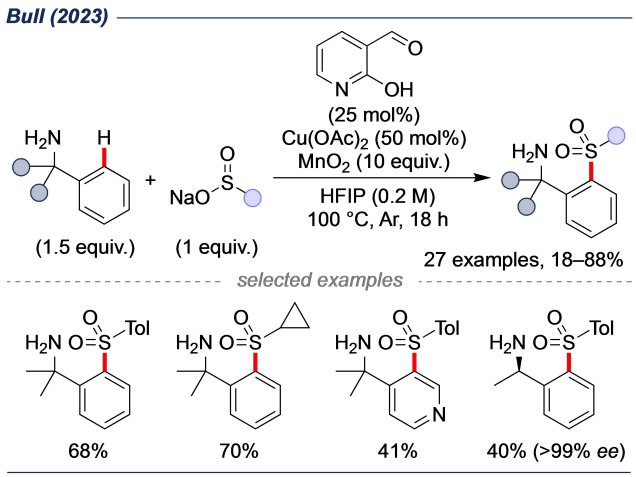
Amine functionalization poses unique challenges for C–H functionalization, which has impacted the extent to which it has been explored. An *exo* imine directing group is formed *in situ* by the condensation of the amine substrate and either an aldehyde,[32] acetal[33] or ketone additive.[29] While a free amine can direct C–H activation in some circumstances, it can be more effective to use a transient imine strategy. Advances in amine functionalization remain less extensively explored, with several examples employing high carbonyl additive loadings (> 50 mol%) to achieve C–O and C–F bond formation.[34]

A seminal example of C(sp^3)-H amine functionalization was reported by Yu in 2016, in which cyclohexylamine was arylated in the γ-position by palladium catalysis (Scheme 8).[35] This example remains the most efficient system in terms of turnover of the TDG, with as little as 4 mol% affording the arylated product in 61% yield. The high efficiency with regard to the TDG is likely achieved by a combination of the high catalytic competency of 2-hydroxynicotinaldehyde[35,36] and the use of water as an additive in concert with HFIP and AcOH. The addition of water has been important in amine functionalization, but is not common in the corresponding amine or ketone works.

A recent advance in amine functionalization from Messaoudi involved the C–H arylation of glycosyl amines (Scheme 8).[37] This powerful advance, while requiring a high catalyst loading (50 mol%), allows the functionalization of glycosides. These challenging substrates possess multiple coordinating sites which must be overcome to achieve C–H functionalization,



Scheme 8. Palladium catalysed arylation of amines.



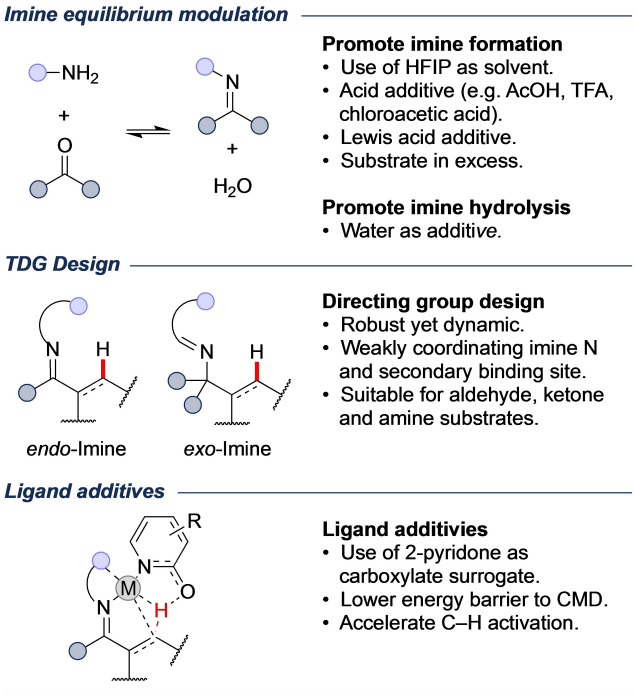
Scheme 9. Sulfonylation of benzylamines in a copper catalyzed transient directing group approach.

which necessitates the high additive loading. *In situ* azidation allowed the isolation of the glycosyl azide directly.

Unlike in carbonyl functionalization, the use of palladium catalysis has until recently been the only metal explored for transient C–H functionalization of amines. We (Bull) demonstrated the use of a copper catalyzed method for the transient C(sp^2)-H sulfonylation of amines (Scheme 9).[38] By the use of co-catalytic 2-hydroxynicotinaldehyde and copper acetate, the sulfonylation of benzylamines was achieved in up to 88% yield, using manganese oxide as the terminal oxidant and base. Similar to earlier work achieving aldehyde functionalization, the use of HFIP was key to achieving any reactivity, and enhanced yield was observed by use of the amine in a slight excess.

5. Conclusions and Outlook

Since the earliest examples of cyclometallation using stoichiometric imines to state-of-the-art transient directing group methods, the field of directed C–H functionalization continues to advance rapidly. This concept article has highlighted the necessary criteria for an imine directing group to be considered 'transient', namely: dynamic TDG formation/cleavage, no discrete DG installation or removal steps and the possibility for catalysis. Recent TDG strategies have used a low catalytic loading the imine forming additive. This can be achieved by three main strategies: i) direct control of imine equilibrium, ii) improved design of the TDG, and iii) the use of additional ligand additives to speed up sluggish steps and ensure good rate matching of imine formation and C–H functionalization (Scheme 10). Commonly, fluorinated solvents, like HFIP, are used in concert with acid additives to control the imine equilibrium. Alternately, water is added to ensure rapid turnover of the TDG if it is trapped as the product imine. The most common TDG design involves the inclusion of an acidic weakly coordinating second binding site (i.e. CO_2H or phenolic



Scheme 10. Common strategies to achieve a catalytic TDG.

OH) to both ensure facile imine formation and to effectively bind the metal. Finally, the use of ligand additives has unlocked certain reactivities by lowering the energy barriers of key transition states.

Recent developments have uncovered important mechanistic insight through experimental and computation methods, leading to new advancements to expand the scope of this methodology to a much wider range of otherwise unreactive C(sp^3)-H substrates with low directing group additive loadings. While palladium catalysis remains the most popular option in transient directing group mediated C–H functionalization, new advances have extended this synthetic concept to other transition metals which will unlock many potential avenues for future research. We expect this field will continue to expand rapidly to uncover new reactivities, more sustainable reaction conditions and to improve functional group tolerance to realize the potential for late-stage functionalization of complex substrates.

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Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

Keywords: C–H functionalization · Catalysis · Imine · Transient Directing Group

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