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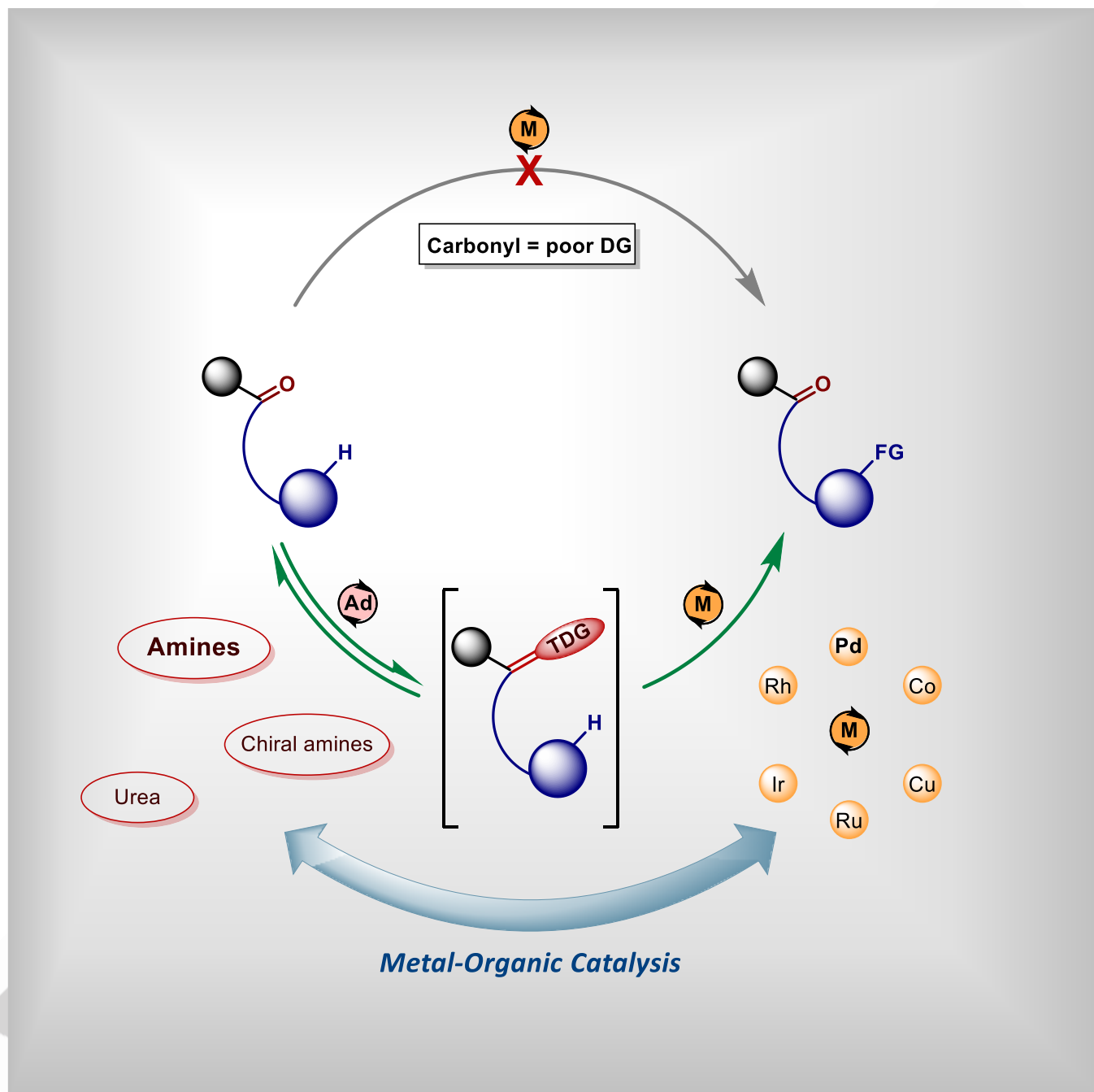
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C–H Functionalization of Aldehydes and Ketones with Transient Directing Groups: Recent Developments

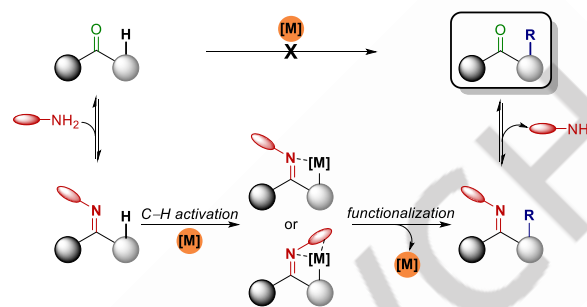
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Abstract: In order to directly functionalize C–H bonds of complex molecules and, in particular, to control the regioselectivity of the reaction, a wide range of directing groups has been used. However, these directing groups need to be installed and removed for further applications, which may limit the use of C–H activation in synthesis. Concerning aldehydes and ketones, a transient directing group strategy has recently emerged to overcome this drawback. The addition of an additive, in general an amine, allowed the *in situ* formation of the real directing group to achieve C–H activation. This review presents the latest developments in the field over the period 2020–2023.



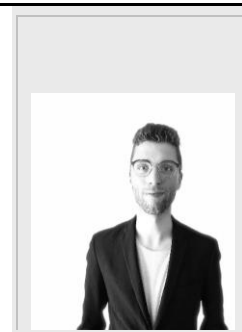
Scheme 1. C–H activation of carbonyl derivatives based on a TDG strategy.

1. Introduction

Since the early 2000's, C–H activation has attracted a lot of chemists and the field has witnessed many improvements.^[1] In particular, the possibly used directing groups (DGs) have significantly evolved. Indeed, strongly coordinating DGs, such as phosphine or nitrogenated heterocycles, were initially employed to form a stable metallacycle *via* C–H activation, which could then react to deliver newly functionalized products.^[2] However, these DG are often very difficult to remove or transform, thus these C–H functionalization methodologies were barely applied in synthesis. To avoid this drawback, the use of weakly coordinating DG such as carbonyl derivatives has emerged in the 2010's.^[3] With this family of DGs, C–H activation reactions can be harder to achieve because of the formation of a less stable metallacycle intermediate. Nevertheless, further transformations and synthetic applications are much more diverse.^[4] Among carbonyl derivatives, many methodologies have been developed for amides because of the possibility to have a bidentate DG (such as with 8-aminoquinoline),^[5] but aldehydes are in general far more challenging substrates.^[6] Due to the importance and the versatility of aldehydes, researches on direct C–H functionalization with the addition of an amine, to form a more efficient DG, appeared (Scheme 1). In this strategy, an amine is added into the reaction to generate an imine *in situ* which plays the role of DG, monodentate or bidentate in function of the amine, for the C–H activation step. The metal-catalyzed C–H functionalization then takes place on the imine derivative and the newly functionalized aldehyde is finally delivered while regenerating the amine. In this approach, a labile transient directing group (TDG) is formed to achieve the C–H activation without any additional steps or DG manipulation. Moreover, enantiopure amines can be employed and so asymmetric transformations can be realized.

Following the first example of TDG reported by Jun's group on rhodium-catalyzed hydroacylation of alkenes,^[7] rhodium was the metal of choice to achieve such transformations. However, since 2016 and pioneering work of Yu's team on C(sp³)–H bonds functionalization,^[8] palladium became a promising metal and nowadays a wide variety of metals could be successfully used as catalyst. This area of TDG has recently rapidly expanded and has been the subject of various reviews focusing on specific aspects.^[9] This review is presenting recent advances (2020–2023) of carbonyl derivatives (ketones and aldehydes) C–H functionalization based on TDG strategy. The functionalization of C(sp²)–H bonds will be first discussed by dividing between aromatic and non-aromatic C–H bonds. Then, a second part will focus on C(sp³)–H bonds, separated between benzylic and non-activated C–H bonds. In addition, this manuscript has been ordered according to the metal employed for the C–H activation reaction.

Hugo Amistadi-Revol studied chemistry at CPE Lyon where he graduated in 2021. During his last year of Master, he went to University College of London to join the group of Prof. H. Hailes. In 2021, he started his PhD under the supervision of Dr. S. Prévost at ENSTA Paris where he is working on C–H activation methodologies on naphthalene skeleton and their applications in synthesis.

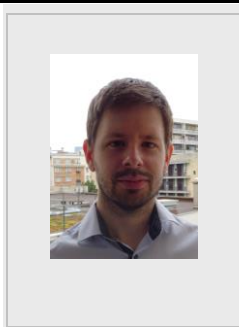


REVIEW

Shanshan Liu received her B.S. degree from Dalian University in 2018 and her M.S. degree in chemical engineering from Shanghai Institute of Technology in 2021 under the supervision of Prof. Sheng Han and Prof. Han Yu. In 2021, she obtained a CSC fellowship to conduct Ph.D. studies at ENSTA Paris under the supervision of Prof. Laurent El Kaïm and Dr. Sébastien Prévost where she is working on C–H functionalization thanks to transient directing group strategy.



Dr. Sébastien Prévost studied chemistry at ESPCI Paris and, then, obtained his PhD in 2011 under the supervision of Dr. Phannarath Phansavath and Dr. Virginie Vidal at Chimie ParisTech. After two post-doctoral positions in the groups of Prof. Benjamin List (Max-Planck-Institut für Kohlenforschung) and Prof. Varinder Aggarwal (University of Bristol), he was appointed in 2015 as CNRS researcher. His research group mainly focuses on C–H activation methodologies and their application in synthesis.



2. C(sp²)–H functionalization

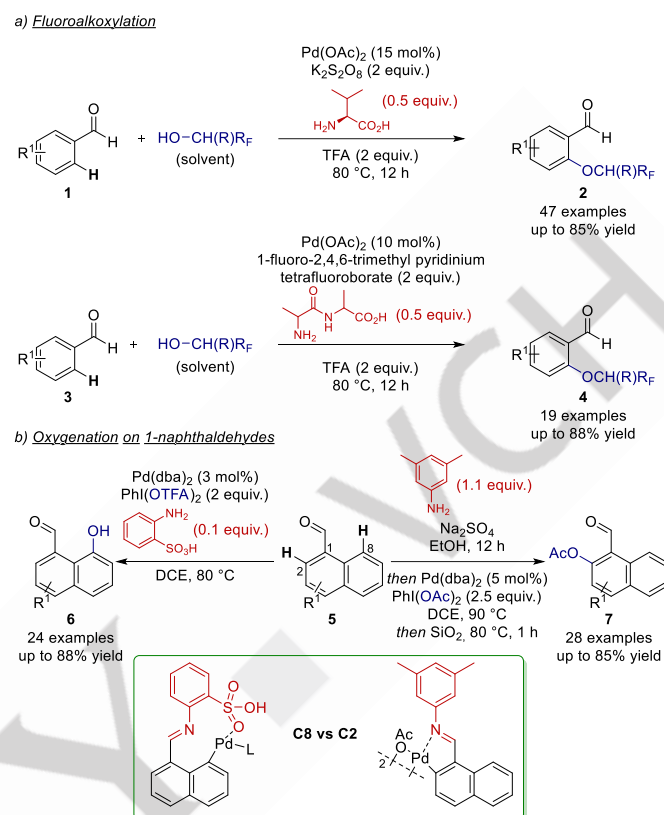
2.1. Functionalization of aromatic C(sp²)–H bond

C(sp²)–H functionalization of aromatic aldehydes and ketones *via* TDG has been extensively studied and can be considered as an efficient method to synthesis polyfunctionalized aromatic building blocks bearing an aldehyde or a ketone moiety. In this part, we will present the recent improvements starting with aromatic aldehydes and then with ketones.

2.1.a. Aldehydes:

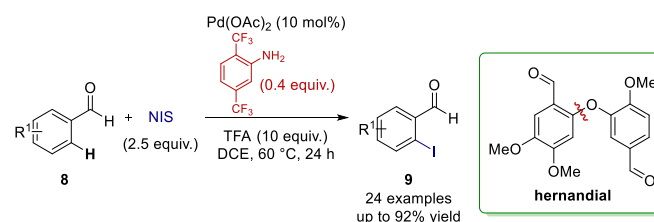
Ortho C–H functionalization of aromatic aldehydes using TDG has been well described by a lot of research groups. Initially, advances were achieved on arylation and halogenation reactions,^[9] but, in the recent years, the variety of possible introduced groups increased. For instance, in 2021, Wang's group developed a palladium-catalyzed fluoroalkoxylation reaction of benzaldehydes **1** using valine to form the TDG and different fluorinated alcohols as ether provider (Scheme 2.a).^[10] Similar conditions were recently proposed but this time with an amino-amide as TDG precursor.^[11] Another palladium-catalyzed oxygenation reaction was described by Zhang's group specifically on 1-naphthaldehydes (Scheme 2.b).^[12] They were able to switch the regioselectivity of the reaction in function of the imine intermediate. When a bidentate TDG was generated thanks to orthanilic acid, a C8–H oxygenation was observed, whereas monodentate aromatic imine, synthesized with 3,5-dimethylaniline and isolated, directed the oxygenation towards the C2 position. In addition, DFT calculations were performed to explain the regioselectivity of the reaction and to support a

proposed mechanism which is going through two different palladacycle intermediates.



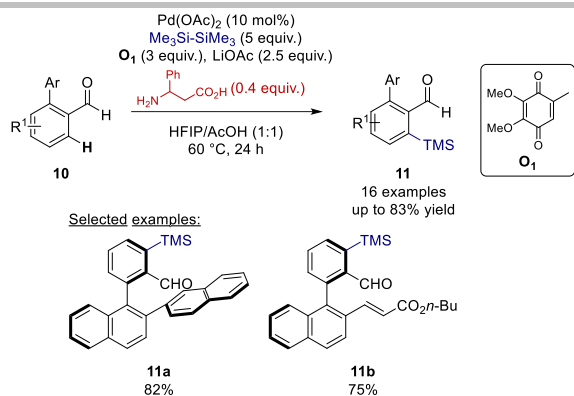
Scheme 2. C–H oxygenation reactions.

In 2021, Zhang and Zhou reported a palladium-catalyzed *ortho*-C–H iodination of aromatic aldehydes involving a monodentate TDG (Scheme 3).^[13] Very useful 2-iodobenzaldehydes **9** were obtained in good yields and the methodology was applied to a two-step synthesis of hernandial through a copper-catalyzed coupling reaction with 2-iodo-4,5-dimethoxybenzaldehyde.

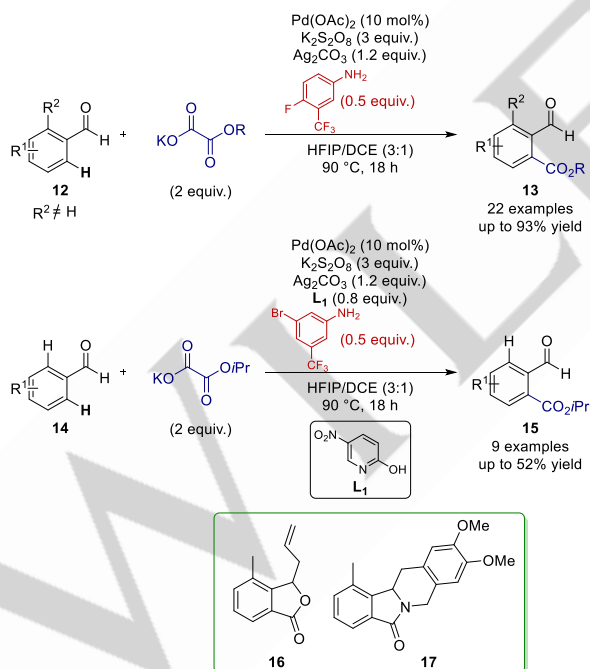


Scheme 3. *Ortho*-C–H iodination.

The scope of the *ortho*-C–H functionalization of aromatic aldehydes with TDG was extended by Shi's group who developed a palladium-catalyzed silylation of biaryl aldehydes **10** with a catalytic amount of 3-amino-3-phenylpropionic acid to form a bidentate TDG and hexamethyldisilane as silicon source (Scheme 4).^[14] This reaction was successfully applied to different axially chiral biaryl aldehydes.

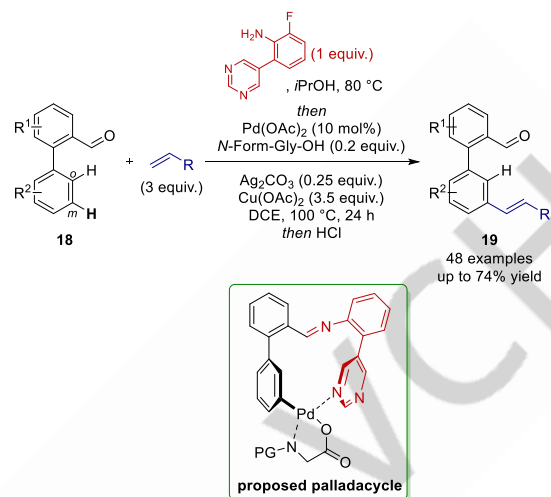
Scheme 4. *Ortho*-C–H silylation of biaryl aldehydes.

Very recently, our team (Prévost) disclosed a palladium-catalyzed C–H alkoxycarbonylation of aromatic aldehydes, using potassium oxalate monoesters as ester provider, to efficiently deliver 2-formyl benzoates (Scheme 5).^[15] 4-Fluoro-3-(trifluoromethyl)aniline was able to form efficiently a monodentate TDG and corresponding esters **13** were isolated in very good yields from *ortho*-substituted benzaldehydes. The reaction conditions were reoptimized for non-*ortho*-substituted aldehydes to avoid difunctionalization and another aniline as well as a 2-pyridone ligand **L**₁ were necessary to obtain expected esters **15** in moderate yield. This reaction was applied to the synthesis of phthalide **16** or isoindolinone **17** after nucleophile addition.

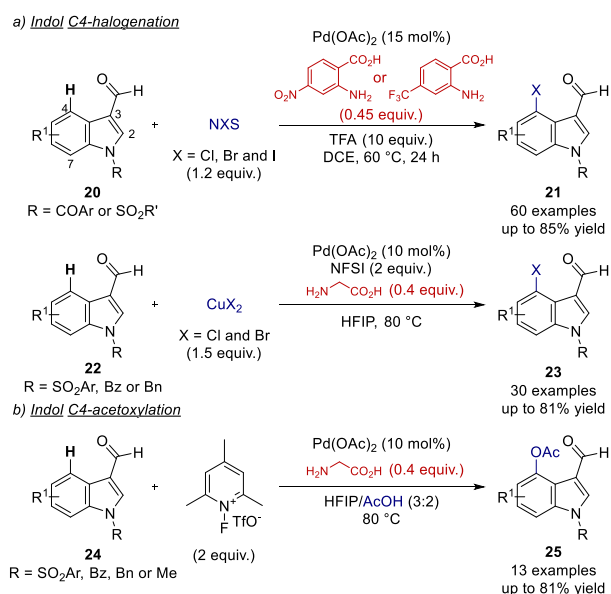
Scheme 5. *Ortho*-C–H alkoxycarbonylation of benzaldehydes.

Ortho-C–H functionalization is now well described so Maiti's group tackled the regioselectivity challenge. Employing a pyrimidine-based aniline to reach the *meta*-C–H bond, alkenylation of biphenyl aldehydes **18** was realized in moderate to good yields (Scheme 6).^[16] A palladium-macrocylic transition

state due to an extended TDG was proposed to explain the selectivity. This reaction, where *meta*-C–C bonds are formed without any DG manipulation, opens the door to regioselective multiple functionalizations of aromatic aldehydes.

Scheme 6. *Meta*-C–H alkenylation of biphenyl aldehydes.

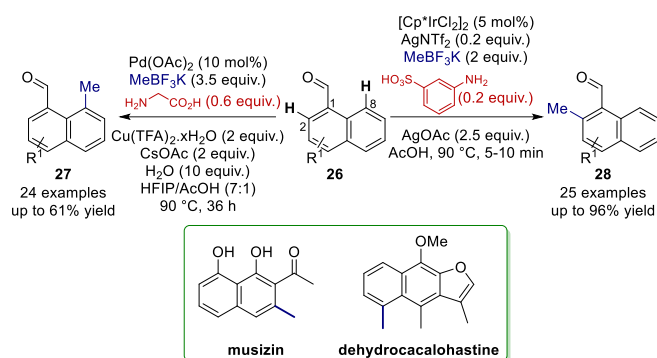
In order to extend the possibilities of the TDG strategy, some research groups focused on different scaffolds, in particular indol derivatives. In 2021, Zhou proposed a C4-halogenation of protected indol-3-carbaldehydes **20** (Scheme 7.a). Despite the presence of several potentially activatable C–H bonds (C2–H, C4–H, C7–H and on the protecting group), only C4-halogenated protected indols **21** were synthesized thanks to anthranilic acids to form the TDG.^[17] Later, similar C4-functionalization was described by Volla's group but this time with glycine as additive amine.^[18] A C4-halogenation was achieved using CuX₂ as halide source as well as a C4-acetoxylation because of acetic acid as the acetate source (Scheme 7).



Scheme 7. C4-functionalization of indols.

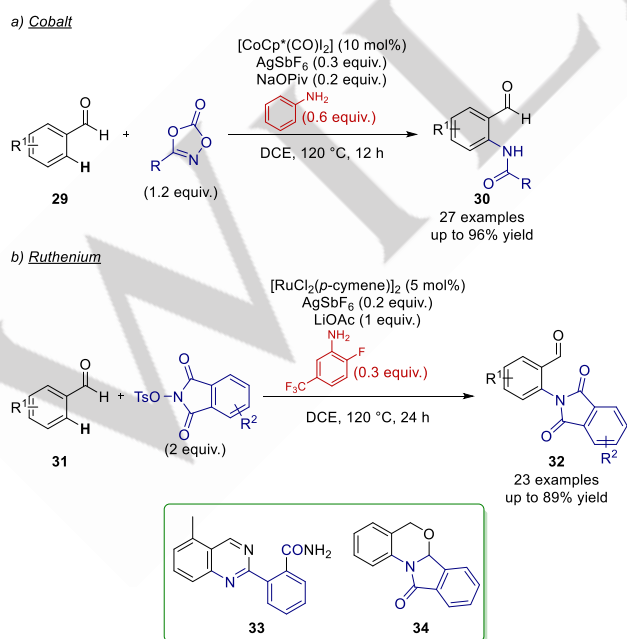
REVIEW

For their part, Hu and Zhang were interested in 1-naphthaldehydes. After having developed an oxygenation reaction (Scheme 2.b), a regioselective C2- or C8-methylation was reported involving a palladium catalysis with glycine to form the TDG to achieve a C8-selectivity and a combination of iridium catalyst with metanilic acid for the C2-functionalization (Scheme 8).^[19] Mechanistic studies as well as DFT calculations were performed to explain the regioselectivity and this methodology was successfully applied to the synthesis of natural products such as musizin or dehydrocacalohastine.^[20]



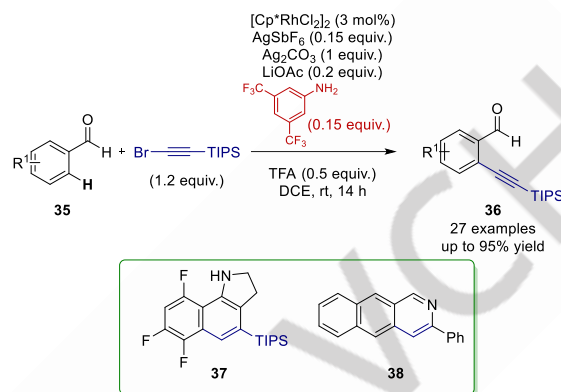
Scheme 8. Regioselective methylation of 1-naphthaldehydes.

As shown previously with iridium, transition metals other than palladium could be used for TDG C–H activations. For instance, Sundararaju's group developed a cobalt(III)-catalyzed amidation reaction with aniline to form the TDG (Scheme 9.a).^[21] This kind of transformation was also proposed with a ruthenium catalyst by Zhou and Zhang who achieved an *ortho*-C–H imidation reaction of benzaldehydes **31** (Scheme 9.b).^[22] Products could be easily converted into nitrogenated heterocycles such as quinazoline **33** or isoindolinone **34**.



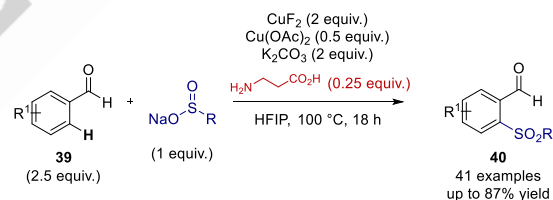
Scheme 9. Metal-catalyzed amidation and imidation.

In 2021, Echavarren's group described a rhodium-catalyzed alkylation of aromatic aldehydes **35** with bromo-alkyne as alkyne provider (Scheme 10).^[23] This strategy allowed an access to very useful benzaldehyde products **36** bearing an alkyne moiety in *ortho*-position in very good yields and could be applied to the synthesis of different polyaromatic heterocycles such as indoline **37** or isoquinoline **38**.



Scheme 10. Rhodium-catalyzed alkylation.

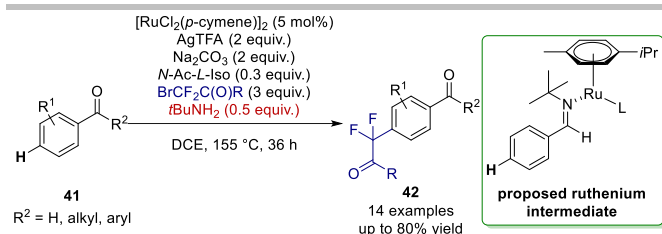
Most of the time, precious metals were used to achieve transformations involving TDG. However, in 2022 the group of Bull reported the first use of a TDG in combination with a copper complex. A copper-mediated sulfonylation of benzaldehydes **39** was described utilizing a catalytic amount of β -alanine (Scheme 11).^[24] In this reaction, copper fluoride had the role of copper source as well as oxidant.



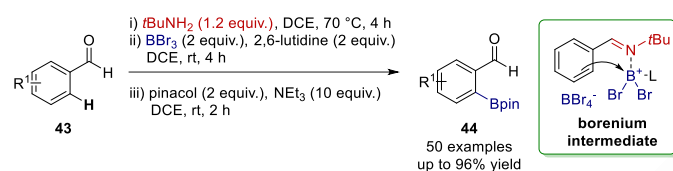
Scheme 11. Copper-mediated sulfonylation.

Interestingly, An and Li recently described a *para*-selective C–H difluoroalkylation with a ruthenium catalyst (Scheme 12).^[25] The reaction was successful with aromatic aldehydes and ketones employing *tert*-butylamine as key amine additive. Some mechanistic experiments were carried out to explain the *para*-selectivity, and a mechanism involving a ruthenium complex where the ruthenium is only coordinated to the nitrogen of the imine moiety was proposed. Then, the addition of a radical, generated from 2-bromo-2,2-difluoroacetate, onto the less sterically hindered position of this intermediate allowed the formation of the *para*-product.

REVIEW

Scheme 12. Ruthenium-catalyzed *para*-difluoroalkylation.

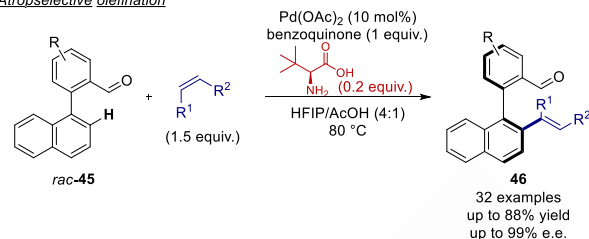
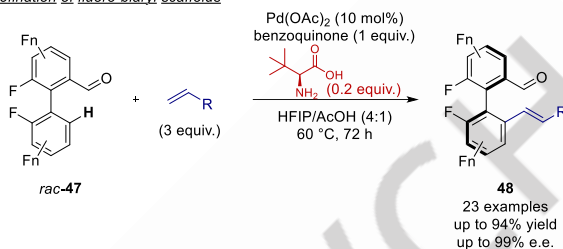
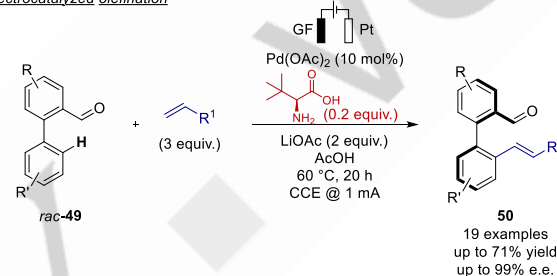
A last example of C–H activation involving TDG was proposed by Chatani's group who developed a metal-free C–H borylation of aromatic aldehydes **43** (Scheme 13).^[26] In this reaction, the imine DG coordinates to the boron atom which can direct an electrophilic aromatic substitution to the *ortho*-position via the proposed borenium intermediate.



Scheme 13. Metal-free borylation.

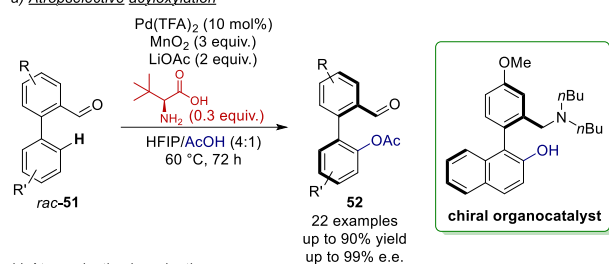
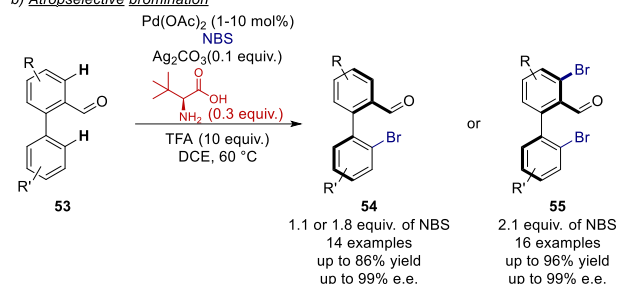
Different kind of amines have been used to form TDG and in particular amino-acids. Therefore, some research groups focused on the development of asymmetric transformation involving chiral TDG.^[27] This strategy allows efficient access to atropisomers or chiral cycles.

The most studied reaction to generate atropisomers from biaryl aldehydes is probably the olefination reaction. These reactions involved kinetic resolution processes to obtain only one enantiomer of the olefinated biaryl thanks to a chiral amino-acid, generally *L-tert*-leucine. Recently, Sharma's group disclosed a palladium-catalyzed enantioselective C–H olefination of biaryl aldehydes **rac-45**, especially using maleimides (Scheme 14.a).^[28] In function of the aldehyde, a dynamic kinetic resolution or a kinetic resolution could occur. Similar reaction was applied to fluorinated biaryl aldehydes **rac-47** by Feng and Liu and tetra *ortho*-substituted enantiopure biaryls **48** were synthesized in high yields and excellent enantioselectivities (Scheme 14.b).^[29] Finally, Ackermann's group combined chiral TDG with electrochemistry to avoid chemical oxidant. Once again, olefinated atropisomers **50** were obtained in good yields and enantioselectivities and were used as helicene precursors (Scheme 14.c).^[30]

a) *Atropselective olefination*b) *Olefination of fluoro-biaryl scaffolds*c) *Electrocatalyzed olefination*Scheme 14. Synthesis of atropisomers *via* enantioselective olefination.

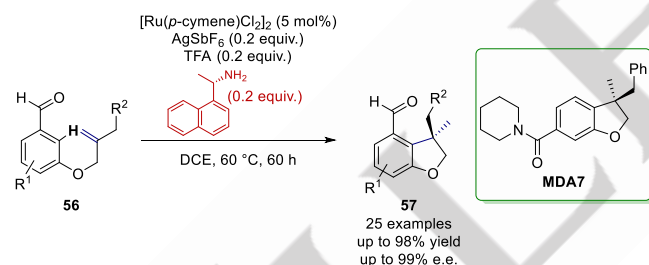
Initially, only reactions creating C–C bonds (olefination, alkylation, alkynylation or arylation) were described but, in 2022, Zhang, Wu and Xie developed an atropselective C–H acyloxylation of biarylaldehydes **rac-51** (Scheme 15.a).^[31] This method was applied to the synthesis of an axially chiral amino-phenol organocatalyst which was used in an asymmetric diethylzinc addition onto aldehydes. Very recently, Rezayee's team achieved atropselective brominations with NBS as brominating agent (Scheme 15.b).^[32] In function of the amount of NBS, mono- or dibromination were observed and the chiral brominated biaryls were used in the synthesis of several enantiopure biaryl scaffolds.

REVIEW

a) *Atropselective acyloxylation*b) *Atropselective bromination*

Scheme 15. Recent atropselective transformations with chiral TDG.

In addition of atropisomers, enantiopure cycles could be synthesized thanks to chiral TDG. Wang's group developed an enantioselective intramolecular hydroarylation of olefin to form 2,3-dihydrobenzofurans **57** bearing a chiral quaternary center (Scheme 16).^[33] In this reaction, (*S*)-1-(1-naphthyl)ethylamine was used to form a chiral TDG and this protocol was applied to the enantioselective synthesis of a CB2 receptor agonist, MDA7.

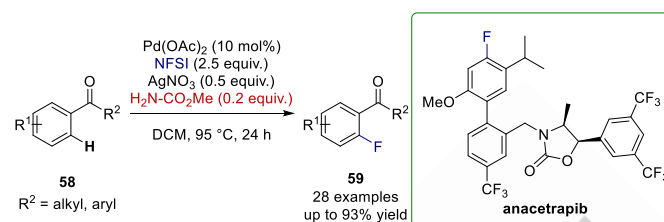


Scheme 16. Ruthenium-catalyzed synthesis of enantiopure 2,3-dihydrobenzofurans.

2.1.b. Ketones

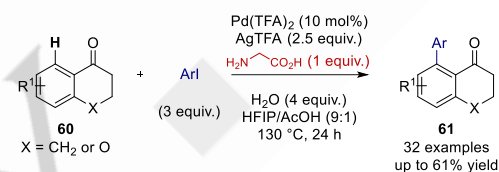
Ketones are generally more challenging substrates than aldehydes because of their lower electrophilicity and their greater steric hindrance which makes the formation of the TDG more difficult. Moreover, although ketones have a weak coordinating ability and required generally harsh conditions for C–H activation, they are less sensitive than aldehydes so can be more often used as real DG.^[34] However, some examples of C(sp²)–H activation of ketones based on a TDG strategy have been reported. Previously, arylation or amidation reactions were described and, in 2021, Lou and Xu disclosed a palladium-catalyzed fluorination of aromatic ketones **58** with methyl carbamate to form a TDG (Scheme 17).^[35] A wide range of fluorinated ketones **59** were obtained in good yields and the strategy was applied to a formal synthesis of

anacetrapib, a cholesteryl ester transfer protein inhibitor developed by Merck.



Scheme 17. Palladium-catalyzed fluorination of aromatic ketones.

Prim's group was interested in the palladium-catalyzed arylation of benzo-fused cycloalkanones **60** with aryl iodides. The reaction was successful with the need of one equivalent of glycine and DFT calculations were performed to propose a full mechanism (Scheme 18).^[36]

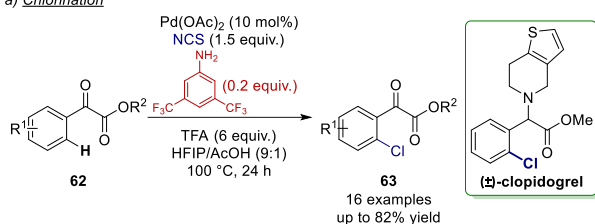


Scheme 18. Palladium-catalyzed arylation of benzo-fused cycloalkanones.

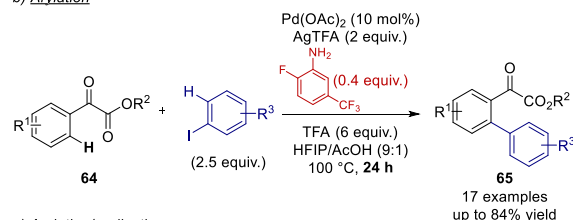
For their part, Zhang's group focused on α -ketoesters. They first developed a palladium-catalyzed chlorination reaction and applied it to the synthesis of clopidogrel (Scheme 19.a).^[37] On this class of substrates, an arylation reaction was described and, in function of the reaction time (24 h or 48 h), *ortho*-arylated products **65** (Scheme 19.b) or cyclized 9-fluorenoles **67** (Scheme 19.c) were isolated.^[37,38] Very recently, the same group achieved an iridium-catalyzed amidation reaction with sulfonyl azides as nitrogen source (Scheme 19.d).^[39] The synthesized amido-esters **69** could be converted in one step into complex heterocycles such as isatin **70** or 1,2-dihydroquinoline **71**.

REVIEW

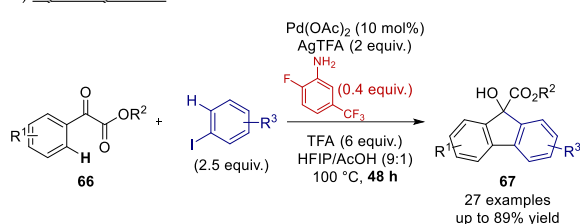
a) Chlorination



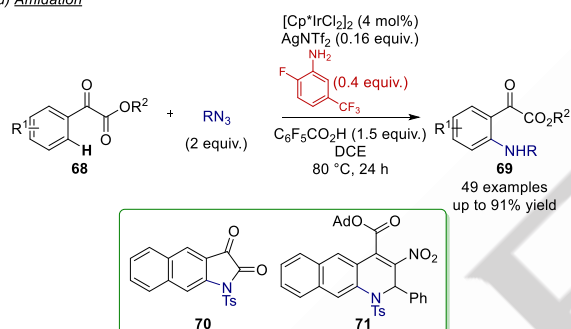
b) Arylation



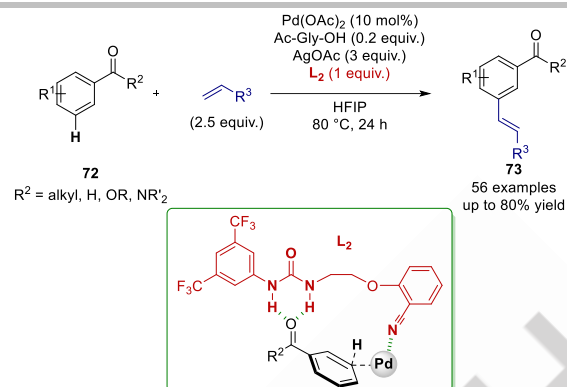
c) Arylation/cyclization



d) Amidation

Scheme 19. *Ortho*-C–H functionalization of α -ketoesters.

Recently, a strategy based on non-covalent interactions starts to emerge in C–H activation.^[40] In this approach, a ligand is added to form a TDG, *via* hydrogen bonding or ion pairing interactions with the substrate, which will control the metal approach. In 2021, Xu and Jin disclosed a *meta*-selective olefination of aromatic carbonyl derivatives **72** based on this strategy.^[41] A bifunctional urea bearing a nitrile moiety was used to control the C–H activation. On one side, the urea moiety forms H-bonding with the carbonyl group and, on the other side, the nitrile moiety directs the approach of the palladium catalyst toward the *meta*-position (Scheme 20). *Meta*-olefinated carbonyl derivatives **73** were obtained in good yields and regioselectivities despite one equivalent of bifunctional urea **L**₂ was required.

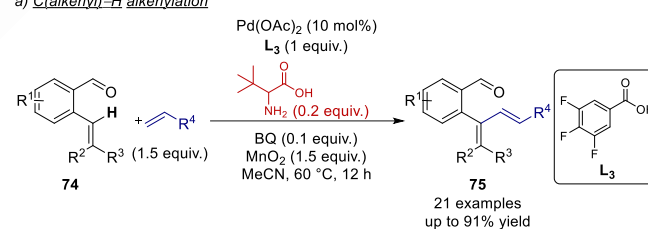
Scheme 20. *Meta*-C–H olefination due to noncovalent H-bonding interactions.

In this chapter, recent advances in aromatic C(sp²)–H bond functionalizations of carbonyl derivatives were described. This is the majority of the examples but other types of C–H bonds have been functionalized thanks to TDG.

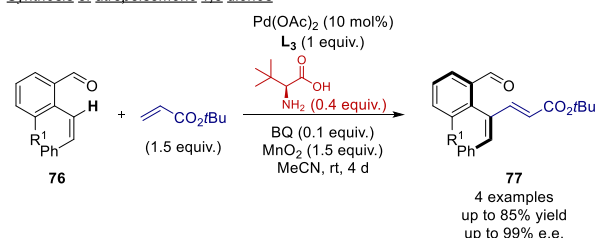
2.2. Functionalization of non-aromatic C(sp²)–H bond

After having developed enantioselective hydroarylation and fluoroarylation of alkenyl aldehydes with chiral TDG,^[42] the group of Engle disclosed in 2022 a palladium-catalyzed alkenylation of alkenyl aldehydes **74** (Scheme 21).^[43] In this work, *tert*-leucine was used to form TDG and to synthesize 1,3-dienes **75** with an excellent *E/Z*-selectivity. The addition of benzoic acid derivative **L**₃ as palladium ligand was necessary to enhance the reactivity. Moreover, the reaction was realized on 3-substituted 2-alkenyl benzaldehydes **76** with *L-tert*-leucine and enantioenriched axially chiral dienes **77** were obtained with excellent enantioselectivities (Scheme 21.b).

a) C(alkenyl)–H alkenylation



b) Synthesis of atropisomeric 1,3 dienes



Scheme 21. Palladium-catalyzed C(alkenyl)–H activation.

This first example of C(alkenyl)–H functionalization allowed an access to complex aldehydes with synthetic applications and will probably encourage further research on this topic.

REVIEW

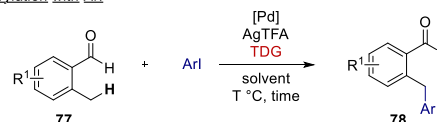
3. C(sp³)–H functionalization

We have seen a large number of examples of C(sp²)–H functionalization in the previous chapter but C(sp³)–H bonds were also successfully activated thanks to TDG strategies. We will now focus on this type of C–H bonds which are generally more challenging. This section is divided into two parts: one axed on benzylic bonds and a second one on non-activated C(sp³)–H bonds.

3.1. Functionalization of benzylic C(sp³)–H bond

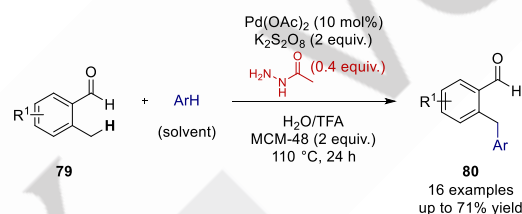
Since pioneering work of Yu's group on arylation,^[8] several research groups focused on benzylic C–H activation thanks to TDG strategy. The challenge in this kind of reaction is to find the suitable TDG in order to favor the benzylic functionalization over the aromatic one. The arylation reaction has been the most studied one and many conditions have been reported (Scheme 22). Traditionally, conditions involved a palladium catalyst with silver trifluoroacetate, an aryl iodide as aryl source and different TDG (Scheme 22.a). In 2020, Li's team found that it was possible to use semicarbazide to form a TDG which directed the benzylic arylation.^[44] Two other reports have shown the feasibility of the reaction with 2-amino-*N*-methyl-acetamide or 2-dimethylaminoethylamine under similar reaction conditions.^[45,46] In order to improve the catalytic system, Bao's group developed a heterogeneous palladium-catalyzed benzylic arylation thanks to palladium nanoparticles.^[47] The catalyst recyclability was evaluated and the yield started to drop after five cycles. Finally, Wei found that 2-amino-*N,N'*-diisopropylsuccinamide was forming an efficient TDG for benzylic activation of aldehydes and ketones but, in function of the substrate, aromatic arylation was also possible.^[48] Benzylic arylation reaction was also achieved *via* dehydrogenative cross-coupling with electron rich aromatic (Scheme 22.b).^[49] The use of acetohydrazide with potassium persulfate as oxidant exhibited a benzylic regioselectivity whereas a selectivity switch towards aromatic C–H bond was observed with anthranilic acid. In order to extend the scope of the arylation reaction, in particular with *ortho*-substituted aryl iodides which suffer from a lack of reactivity due to steric hindrance, a benzylic biarylation reactions was described with cyclic diaryliodonium salts and *tert*-leucine as TDG (Scheme 22.c).^[50] Through this reaction, complex biaryl products **82** bearing iodine and aldehyde were synthesized and converted into polycyclic aromatic hydrocarbons.

a) Benzylic arylation with ArI

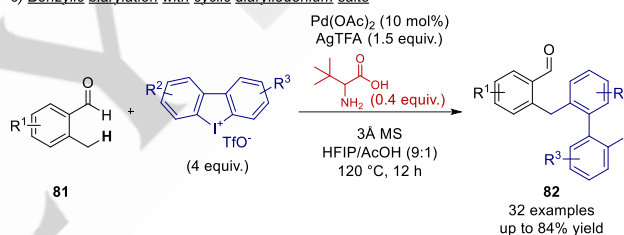


entry	conditions	TDG (equiv.)	Ref.
1	Pd(PPh ₃) ₂ Cl ₂ (10 mol%), AgTFA (3 equiv.), H ₂ O (14 equiv.), <i>n</i> PrCOOH (0.7 M), 120 °C, 48h	(0.3)	43
2	Pd(OAc) ₂ (20 mol%), AgTFA (1.5 equiv.), AcOH/H ₂ O (9:1), 120 °C, 48 h	(0.5)	44
3	Pd(OAc) ₂ (10 mol%), AgTFA (2 equiv.), HFIP, 4A MS, 120 °C, 24 h	(1)	45
4	3 wt% Pd/γ-Al ₂ O ₃ , AgTFA (3 equiv.), AcOH/HFIP (3:1), 130 °C, 48 h	(0.3)	46
5	Pd(OAc) ₂ (10 mol%), AgTFA (1.5 equiv.), TFA, 100 °C, 24 h	(0.5)	47

b) Benzylic arylation via dehydrogenative cross-coupling



c) Benzylic biarylation with cyclic diaryliodonium salts

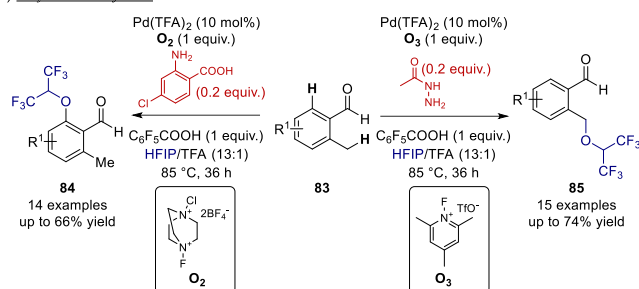


Scheme 22. Benzylic arylation.

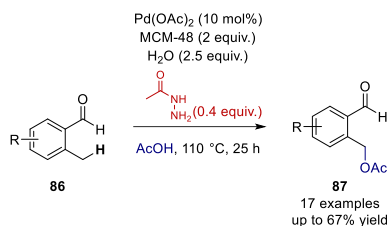
Although benzylic arylation is still the most studied reaction, other functional groups were successfully introduced in benzylic position of aldehydes thanks to TDG. For instance, Bao's group developed a palladium-catalyzed polyfluoroalkoxylation reaction of aromatic aldehydes **83** through the addition of fluoroalcohol (Scheme 23.a).^[51] Once again, the observed regioselectivity of the reaction depended of the TDG and the oxidant. When anthranilic acid and oxidant **O**₂ were used, an aromatic polyfluoroalkoxylation was noticed whereas the benzylic regioselectivity was achieved with acetohydrazide in combination with **O**₃. The same research group also disclosed a benzylic acetoxylation reaction with acetohydrazide as TDG (Scheme 23.b).^[52]

REVIEW

a) Polyfluoroalkoxylation



b) Acetoxylation



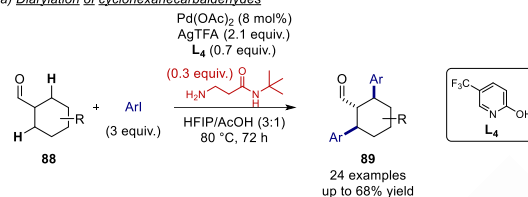
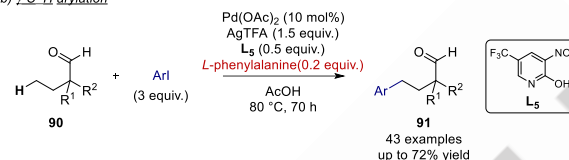
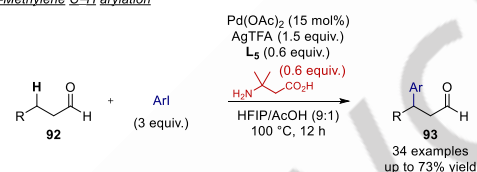
Scheme 23. Benzylic oxygenation.

3.2. Functionalization of non-activated C(sp³)-H bond

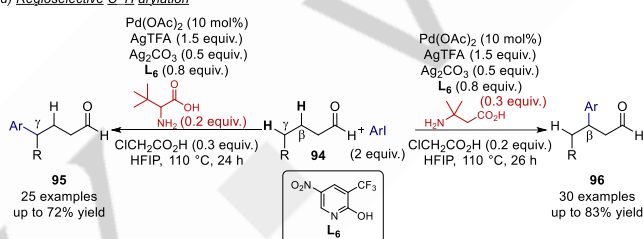
3.2.a. Aldehydes

Since seminal work of Li and Ge,^[53] several improvements on non-activated C(sp³)-H bonds arylation based on a TDG strategy have been reported. Most of these reactions presents similar conditions involving a palladium (II) catalyst, a silver source and 2-pyridinone derivatives as ligand to accelerate the C-H activation step,^[54] whereas the different reactivity is mainly due to the amine used to form the TDG. In 2020, the team of Bull disclosed a diarylation reaction of cyclohexanecarbaldehydes **88** (Scheme 24.a).^[55] A *trans,trans*-stereochemistry was always observed and explained by the formation of an enamine-derived palladacycle (and not an imine as usual) which was responsible of the epimerization of the aldehyde stereogenic center after hydrolysis. Following their work on β -C-H arylation, Li and Ge optimized the conditions and found that the use of phenylalanine as TDG precursor allowed the activation of γ -C-H bonds (Scheme 24.b).^[56] In this case, a [6,5]-bicyclic palladium intermediate was proposed to explain the regioselectivity. Until recently, only methyl or cyclic C-H bonds were successfully activated but, in 2022, Dang, Maiti and Ge reported the first example of palladium-catalyzed methylene β -C-H arylation of primary aldehydes **92** (Scheme 24.c).^[57] Employing 3-amino-3-methylbutanoic acid as TDG, mono- β -arylated primary aldehydes were synthesized in good yield. At the same time, Yu's group reported a regioselective C-H arylation of primary aldehyde **94** and, in function of the employed amine which affects the bite angle of the TDG, β - or γ -arylation was observed (Scheme 24.d).^[58]

a) Diarylation of cyclohexanecarbaldehydes

b) γ -C-H arylationc) β -Methylene C-H arylation

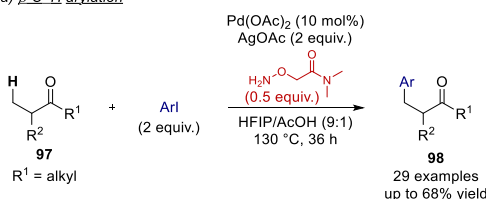
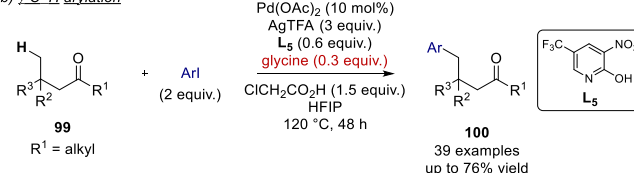
d) Regioselective C-H arylation



Scheme 24. C-H arylation of aliphatic aldehydes.

3.2.b. Ketones

Aliphatic ketones were also used as suitable substrates for C(sp³)-H arylation. Similarly to aldehydes, palladium-catalyzed methyl β -C-H arylation of ketones **97** were described by Liao and Ji with an alkoxyamine (Scheme 25.a).^[59] For his part, Yu's group reported a methyl γ -C-H arylation using glycine for the TDG and pyridine-2-ol **L5** as palladium ligand (Scheme 25.b).^[60]

a) β -C-H arylationb) γ -C-H arylation

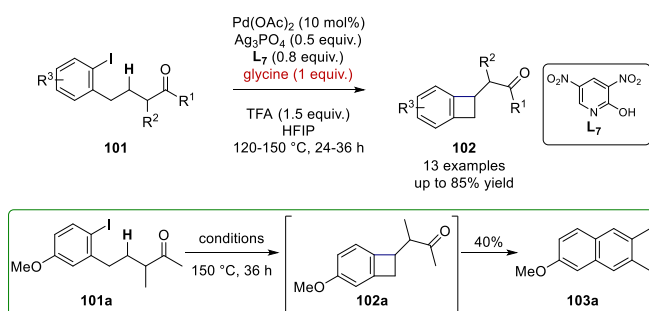
Scheme 25. C-H arylation of aliphatic ketones.

Specific substrate scaffolds were used in such reactions. For instance, Sorensen's group developed an intramolecular arylation reaction of ketones **101** to synthesize benzocyclobutenes **102** (Scheme 26.a).^[61] Interestingly, when a

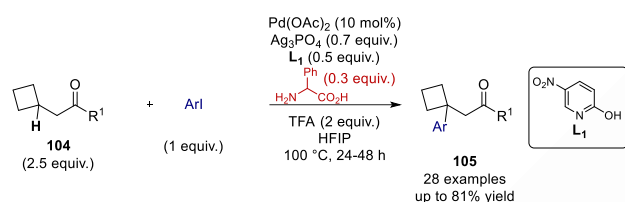
REVIEW

methoxy group was on the aryl moiety, the expected benzocyclobutene **102a** underwent further electrocyclic ring-opening followed by 6π electrocyclization to form a naphthalene ring after water elimination. In 2022, Yu's team focused on C–H arylation of cyclobutylmethyl ketones **104** (Scheme 26.b).^[62] Despite other possible C–H bonds, tertiary C–H bond was regioselectively arylated thanks to phenylglycine as amine additive.

a) Synthesis of benzocyclobutenes

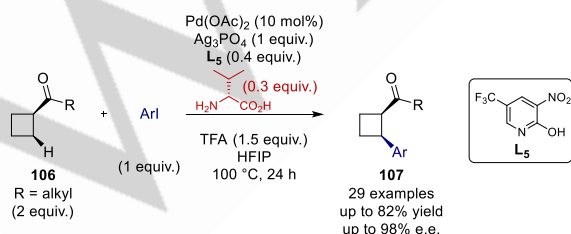


b) C–H arylation of cyclobutylmethyl ketones



Scheme 26. Other C–H functionalizations of aliphatic ketones.

In most of these latter examples, a stereogenic center is created so the use of chiral amino-acid to control this center seems obvious. However, because of the long distance between the TDG and the created stereogenic center, this strategy is very challenging. Impressively, Yu's group disclosed in 2020 a palladium-catalyzed enantioselective arylation of cyclobutyl ketones **106** with the help of a chiral TDG (Scheme 27).^[63] The enantioselectivity was very well controlled thanks to *D*-valine and the combination of L_5 and silver phosphate which were necessary to control the rate-determining step and so reach high enantioselectivities. This method could also be applied to the synthesis of enantiopure trisubstituted cyclobutanes.



Scheme 27. Enantioselective C–H arylation of cyclobutyl ketones.

3. Summary and Outlook

In summary, this review has presented the recent advances on carbonyl derivatives C–H functionalization involving a TDG

strategy. The number of publications on this topic is growing fast, reflecting the interest of the chemical society due to the new possibility to achieve regioselective C–H activation reactions without installing and removing DG. Nowadays, aromatic *ortho*-C–H activation of carbonyl derivatives is well studied and most of the functional groups could be introduced. Enantioselective reactions as well as combination with electrochemistry have been reported. A wide range of metals could be used and several new TDGs have appeared, although high loadings are still often required. Investigations on catalytic systems are still ongoing but future improvements could focus on more challenging regioselectivities (*meta* and *para*) and so the discovery of new TDGs will be necessary. Concerning other type of C–H bonds, research is less advanced. This is especially true for unactivated $C(sp^3)$ -H bonds for which only arylation is known. Due to all research carried out in the area, there is no doubt that the scope of functional groups which can be introduced will grow.

Acknowledgements

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Keywords: Transient directing group • C–H activation • carbonyl derivatives • catalysis • amine

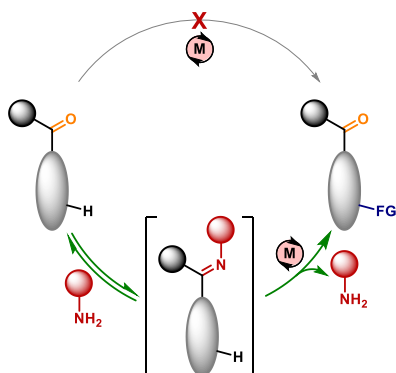
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REVIEW

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Entry for the Table of Contents



Metal-catalyzed C–H functionalization of aldehydes and ketones has recently grown significantly thanks to a concept of transient directing group. In this strategy, the directing group is generated *in situ* which limits the functional group manipulation as well as allows new reactivities. This review presents the latest research works carried out in this area over the period 2020-2023.

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